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ANOMALIES OF THE GASTROINTESTINAL TRACT*

A Review of the Literature and Report of Two Unusual Cases

R. Bretney Miller, M.D.,† and Aubrey O. Hampton, M.D.‡

WASHINGTON, D. C.

MAJOR congenital anomalies of the alimentary tract that produce symptoms are seen almost entirely in infancy and childhood. They are seldom reported in adults. Some of these, such as atresia of the esophagus or other portions of the digestive tract, are inconsistent with continued life. Attempts to remedy these situations pose difficult if not impossible surgical problems. Other anomalies, such as imperforate anus, duplications of portions of the gastrointestinal tract, "congenital bands" and errors of rotation with volvulus, are amenable to successful surgical correction. Still other anomalies are compatible with normal growth and development, do not produce symptoms and may be found only incidentally at operation or autopsy.

A number of excellent reviews have appeared in the literature on the subject prior to 1939. Since that date there have been isolated case reports, though no comprehensive discussion of the subject during the past nine years was found in our search. It seemed of interest, therefore, in connection with the report of 2 additional cases in older patients, to review briefly the subject in general.

The history and literature on anomalies of the digestive tract falls into two general groups: the embryologic features concerned in the production of the anomalies and the clinical considerations and surgical approach to their correction. Meckel,[1] in 1817, was the first to describe the embryology. The studies of Mall[2] in 1898 and those of Frazer and Robbins[3] in 1915 have established the embryology underlying the various malformations that are seen clinically, and thus clarify their etiology. The earliest clinical report was presented in 1827 by Cruveilhier.[4] Thereafter, various cases were described sporadically. Not until 1923, however, did the first comprehensive review of the subject appear. Dott,[5] in a masterly and lucid report, summarized the embryologic and clinical features, adding 3 original cases to 45 collected from the previous literature. (One of these, similar to Case 1 presented below, was reversed rotation volvulus of the ileum, cecum and ascending colon in a sixty-eight-year-old man.) In 1928 Waugh[6] reported an additional 5 cases, all in patients beyond the neonatal period, ranging in age from six-and-a-half to twenty-one years. He stressed the importance of considering congenital anomalies of the digestive tract in the differential diagnosis of the abdominal disorders. Four of his cases were correctly diagnosed prior to operation. Two case reports were added by Raymond and Dragstedt[7] in 1931 in their review of the literature, which brought the total of cases reported to 100. This includes 27 cases of malformations of the colon reported by Hecker, Grunwald and Kühlmann.[8]

In 1933 Ladd[9] described 60 cases of congenital obstruction of the intestine, excluding obstruction caused by bands or hernias or by the various manifestations of Meckel's diverticulum; the obstruction was relieved in 17 cases. In 1936 Ladd[10] reported 620 cases of congenital pyloric stenosis and commented on 53 cases of congenital obstruction of the intestine due to malrotation or nonrotation of the bowel.

In 1934 an excellent discussion and review appeared by Gardner and Hart,[11] who tabulated various features of the individual cases previously reported, adding 2 of their own, bringing the accumulated total to 103 cases. Wakefield and Mayo,[12] in 1936, added 15 new cases, all in adults, the oldest of whom was forty-nine years. In 10 of their cases, there were "congenital bands" as well as malformation of the colon.

McIntosh and Donovan,[13] in 1939, reported 19 additional cases occurring in infants and children.

Embryology

First Stage

About the fifth week, the future alimentary canal, a single tube, suspended by a common dorsal mesentery, begins to divide into the foregut, midgut and hindgut. The midgut grows most rapidly and extends into a physiologic umbilical hernia, at the root of the cord. Between the fifth and the tenth week the first stage of rotation takes place within the cord. The intestine assumes an S-shaped distribution, with the small intestine to the right, the ileocecal junction in the midline and the colon to the left.

*From the Department of Medicine, George Washington University School of Medicine, and the Department of Radiology, Garfield Memorial Hospital.

†Clinical instructor in medicine, George Washington University School of Medicine.

‡Chief, Department of Radiology, Garfield Memorial Hospital.

Second Stage

About the tenth week, the midgut is returned to the abdominal cavity. As the small intestine enters the abdomen, the hindgut and its mesentery are pushed before it to the left and backward (descending colon). The ileum and cecum are last to enter, lying in the midline, free to travel in any direction. Initially, the cecum lies upward and to the right beneath the liver. As the colon further grows and lengthens, the cecum drops to the right lower quadrant. The growth and lengthening of the midgut during the second stage forces a rotation of this part with its mesentery through a counter-clockwise turn of 270° (as one faces the fetus) about the axis of the superior mesenteric artery when the midgut re-enters the abdominal cavity. Normally, the duodenum crosses behind and lies posteriorly, whereas the colon crosses in front and lies anteriorly. Abnormally, failure of rotation causes the small intestine to occupy the right half of the abdomen, with the cecum in the pelvis or left lower quadrant. The colon may be left sided, with a U-shaped bend in the midtransverse portion joining the ascending loop behind and descending loop in front of the stomach. The descending colon and sigmoid (hindgut) are never involved in the faulty rotation. When this abnormal rotation occurs, faulty and imperfect fixation of the intestine is the rule. The ascending colon may have a short mesocolon, with attachment to the left of the vertebral column, or there may be no attachment of the midgut segment.[14-16] Reverse rotation or malrotation in the second stage may occur, giving still other features.

Third Stage

Rotation beginning about the fifteenth week is characterized by further descent of the cecum and fixation and fusion of the mesenteries to the posterior parietal peritoneum. Normally, this proceeds in such a way that displacement with torsions and volvulus are impossible.

Ladd and Gross[17] offer an excellent condensation of the embryologic development:

> From the sixth to the tenth weeks of embryonic life, the alimentary tube grows at a faster rate than does the coelomic cavity, and a portion of the midgut protrudes into the base of the umbilical cord. At about the tenth week the peritoneal cavity grows at a greater rate and the midgut is withdrawn into it. As this recedes into the abdomen it rotates in a counter-clockwise direction (as one faces the fetus). It is therefore evident that the post-arterial portion of the midgut, which includes the terminal ileum, cecum, ascending colon, and transverse colon, lies wholly in the left side of the abdomen. The anti-clockwise rotation continues until the cecum comes to lie in the superior part of the abdomen. Thus, in the eleventh week of fetal life, the cecum and first portion of the colon are in the epigastrium. As the rotation continues, the cecum passes into the right upper quadrant and then finally ends its migration in the right lower quadrant.
>
> After this rotation is completed, the cecum and ascending colon attain peritoneal reflections and attachments in the right side of the abdomen, and the mesentery of the small bowel likewise becomes attached to the posterior abdominal wall from the duodenojejunal junction obliquely downward toward the cecum.

Most of the clinical findings in malrotation of the intestinal tract can be understood if this normal embryology is borne in mind. Arrest of development during the tenth to the eleventh week of fetal life will give rise to anomalies which are characterized by: (1) An incompletely rotated cecum; (2) A lack of attachment of mesentery along the posterior abdominal wall; or (3) A completely rotated cecum which is mobile and unattached.

Anatomy and Pathology

The clinical situations encountered are either one or a combination of the following anatomic findings: volvulus of the entire mesentery, which most often occurs at birth or shortly afterward as the so-called volvulus neonatorum; torsion or volvulus of the ascending colon secondary to abnormal rotation of the midgut loop (as in Case 1); and extrinsic pressure on one or another portion of the intestinal tract, usually the duodenum, from abnormal fixation of the mesentery — this is the so-called "congenital band" (Case 2).

The common lesion underlying the entire pathology is volvulus of any degree with proportionate obstruction. This may arise from insufficient mesenteric attachment (mobile colon and cecum) or from excessive attachments (congenital bands). In the more severe forms, interference with blood supply occurs, with consequent ischemia and later development of necrosis and gangrene in the local segment involved.

Diagnosis

In infants, differentiation is to be made from congenital atresia or stenosis of intestine, intussusception or obstruction from tumors.

In the first few days or weeks of life when congenital aberrations are most prone to produce symptoms, the diagnosis is most frequently suspected. With older children and adults, the diagnosis is often overlooked because this possibility is not considered. In this group a history of abdominal pain preceding or associated with vomiting episodes dating from early childhood is usually obtained. "Indigestion" within the first few months of life is the description usually given to the attacks. These are paroxysmal and often violent. The pain is of the "colicky type" associated with smooth-muscle spasm. However, it has an "unusual" character, as stressed by Waugh,[6] who emphasizes the fact that the associated symptoms have no reference to any of the common or well defined causes of abdominal pain.

Evidence of partial or complete intestinal obstruction may be present, with vomiting, obstipation, inability to pass flatus and abnormally increased peristalsis. Depending on the duration, varying degrees of distention, high-pitched audible or visible peristalsis, local tenderness and a palpable mass may be present individually or in combination. The attack may occur suddenly and

subside in equally sudden manner, leaving only a sense of generalized "abdominal soreness" and no abnormal physical findings. Between the acute episodes the examination is usually entirely negative. However, the presence of an asymmetrical "fullness" on the left side, or of an "emptiness" especially in the right iliac fossa, on inspection and palpation, is an important clue. Waugh[6] stresses this finding as pathognomonic, for all practical purposes, of a left-sided colon, or a subhepatic location of the cecum and terminal ileum. The absence of previous scars of laparotomy or of pelvic operations makes the symptoms and signs much more suggestive of a volvulus from a congenital anomaly rather than obstruction related to previous surgery.

The one laboratory aid of major importance is adequate x-ray examination. Scout films of the abdomen taken in the supine and upright positions may suggest intestinal obstruction from whatever cause by showing gas-distended loops of large or small bowel, containing fluid levels. Fluoroscopy of the colon during examination by means of barium enema, with full-filling, postevacuation and air-contrast films, may prove diagnostic of overfixation, or underfixation with excessive mobility. Waugh[6] has suggested the added maneuver of administration of barium by mouth, fluoroscopically studying its progress in the small bowel, and then giving barium enema to get a composite picture of both small and large bowel on a single film. These technics may elucidate abnormal relations due to "congenital bands" or malpositions of gut, which might not otherwise be demonstrable.

Despite the fact that significant symptoms and signs are present during an attack and that diagnostic aids are available, the diagnosis of a congenital anomaly is too often made at exploratory laparotomy. This is more likely to occur in cases of overfixation and "congenital bands," in which no pathognomonic signs are present, than in the situation of underfixation, as in the "mobile colon," in which definite evidence may be found if properly sought.

Since many cases are discovered accidentally at operation in patients having no symptoms, it is fair to conclude that only a portion of them become clinically important.

Management

The only satisfactory treatment is surgery. The ideal procedure in cases of overfixation with obstruction is the freeing of constricting bands with or without resection of the ischemic segment of bowel as indicated. In the problem of lack of fixation, resection of the abnormally mobile segment, followed by anastomosis to restore normal anatomic relations, is the operative objective. Assuming successful accomplishment and absence of complications, the outlook for permanent relief is excellent.

Case Reports

Case 1. A 49-year-old married woman came under our observation on November 14, 1946. The sole complaint was "repeated attacks of abdominal pain."

Between the ages of 4 and 10 years she had been subject to bouts of "cyclic vomiting." These episodes, forgotten by the patient, were recalled by a physician relative. She had had the usual childhood diseases, with rheumatic fever and chorea at the age of 4, with a recurrence at the age of 19.

Figure 1. *Colon Filled with Barium Showing Excessively Long, Dilated Large Intestine, with the Ascending Colon and Cecum Inverted and the Cecum Lying over the Right-Kidney Area under the Liver.*

Note the twist in the mid-transverse colon, overlying the fourth lumbar vertebra.

After frequent attacks of tonsillitis, the tonsils were removed at the age of 6. Between the ages of 14 and 15½ years she experienced three episodes of pneumonia, once with effusion. There were no sequelae. She was married at the age of 21. She had had 3 initial miscarriages. The 4th pregnancy was terminated for eclampsia. The 5th resulted in a normal delivery. At the age of 48 a polyp of the cervix uteri was removed and reported as benign by histologic examination. There was no history of allergy or typhoid fever, malaria or dysentery.

The patient was the oldest of 5 children. One sister, not living, had experienced recurrent attacks of severe abdominal pain. At exploratory laparotomy, at the age of 22, a "defect of the development of the intestine" was found. The hospital note on this operation revealed "a markedly dilated duodenum and a Jackson's membrane over the ascending colon; the dilated portion of the duodenum was resected and an anastomosis performed between the remaining portion of the duodenum and the proximal portion of the jejunum." Her

father for many years had been subject to recurring bouts of abdominal pain due to severe diverticulitis. Ultimately, surgical resection of a portion of the colon was done, with relief. Two nieces suffered from "megacolon" in childhood. The remainder of the family history was noncontributory.

For at least 25 years the patient recalled acute attacks of abdominal pain at irregular intervals. These appeared to lack any correlation with eating habits, with fatigue or with any activities, although they were more likely to occur after a period of sustained nervous tension. A severe attack began with low-grade discomfort in the middle portion of the abdomen, with gurgling and rumbling. There was a sensation

FIGURE 2. *Detail Spot View of the Mucosal Relief Pattern in the Area of Twist in the Midtransverse Colon. This shows a definite crossing of longitudinal mucosal folds, indicating torsion or volvulus of this segment of gut.*

of "trapped gas and bloating." This progressed to a crampy, colicky pain of "almost unendurable intensity" in a period of several hours. At its maximum, the severe attack was characterized as a terrific "band-like sensation" across the entire upper abdomen that left her "dripping with perspiration and utterly prostrated." Occasionally an attack remained mild and terminated spontaneously. There was no radiation of the pain to the groin, flank, back, chest or shoulder region. There was never any fever; nausea was usually present; vomiting was rare and not a prominent symptom. Obstipation might occur for several hours though flatus was always immediately passed afterward. An enema sometimes appeared to shorten the attack. A regimen of bland, low-residue diet and antispasmodics tended to minimize the frequency, but did not eliminate the attacks. In a full-blown seizure, the only measure affording any real relief, however, was a hypodermic injection of an opiate. This was followed by weakness and exhaustion for several days. The frequency varied from 2 or 3 to 12 to 14 per year. In the intervals between attacks the bowels moved twice daily without laxatives. Her appetite was variable. Food intake was satisfactory both in quantity and in variety; there had been no loss of weight. Her habits were good. A review of the systems failed to reveal other significant symptoms.

Physical examination showed a well nourished and well developed woman, who appeared somewhat younger than her stated age. The weight was 125 pounds, and the height 5 feet, 6¾ inches. Between attacks the physical examination was essentially negative. There was no evidence of any cardiac lesion after the rheumatic fever.

During the attack there was moderate gaseous distention of the abdomen, with no muscle spasm and with moderate tenderness throughout, but most marked in the hypochondrium and periumbilical regions. There was very active peristalsis, with borborygmi audible without the stethoscope.

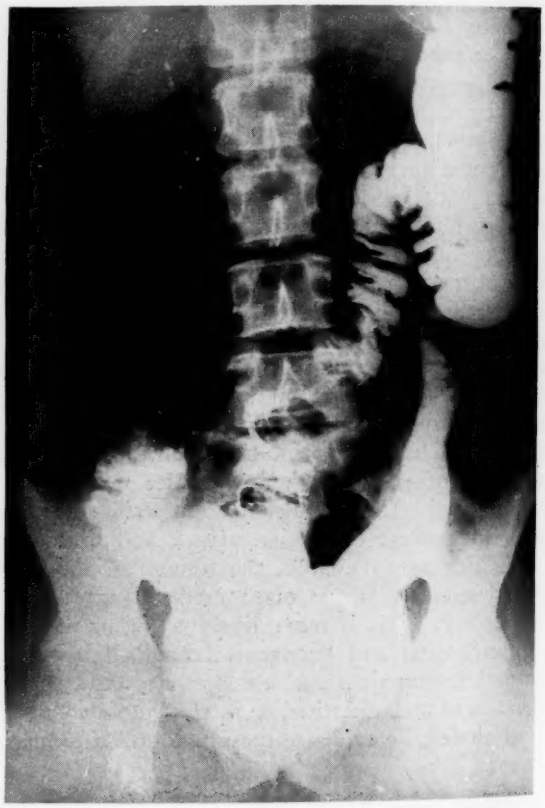

FIGURE 3. *Colon after Evacuation of the Barium Enema. The ascending colon and cecum now lie in the pelvis, having rotated counter-clockwise 180° from their previous position. The point of torsion or volvulus in the transverse colon remains contracted, but the twist in the mucosal folds has disappeared.*

There was never any external herniation. Pelvic and rectal examinations were negative.

The temperature, pulse and respirations were normal. The blood pressure was 130/80.

Urinalysis and leukocyte counts were always negative during the attacks. Interval studies showed the urinalysis to be repeatedly negative. Examination of the blood disclosed a red-cell count of 4,000,000 with a hemoglobin of 12.64 gm. per 100 cc. (75 per cent), and a white-cell count of 9700, with 68 per cent neutrophils, of which 2 per cent were band forms and 66 per cent segmented forms, 2 per cent eosinophils, 26 per cent lymphocytes and 4 per cent monocytes. The

blood smear showed slight variation in the size and shape of the red cells. An electrocardiogram was normal.

X-ray examination (Fig. 1-4) by one of us (A.O.H.) was reported as follows on December 6:

The cervical, dorsal and lumbar spine is essentially normal, as is a cholecystogram with oral dye. A chest film shows the right side of the diaphragm to be fixed in position and flat, consistent with old healed pleurisy. There is no evidence of active disease in either lung field. The heart and great vessels are normal. A plain film of the abdomen is normal, except that the ileum occupies the usual position of the cecum, and ascending colon. Barium enema demonstrates a long, dilated colon. The cecum lies just to the right of the midline, opposite the right kidney. When it is filled

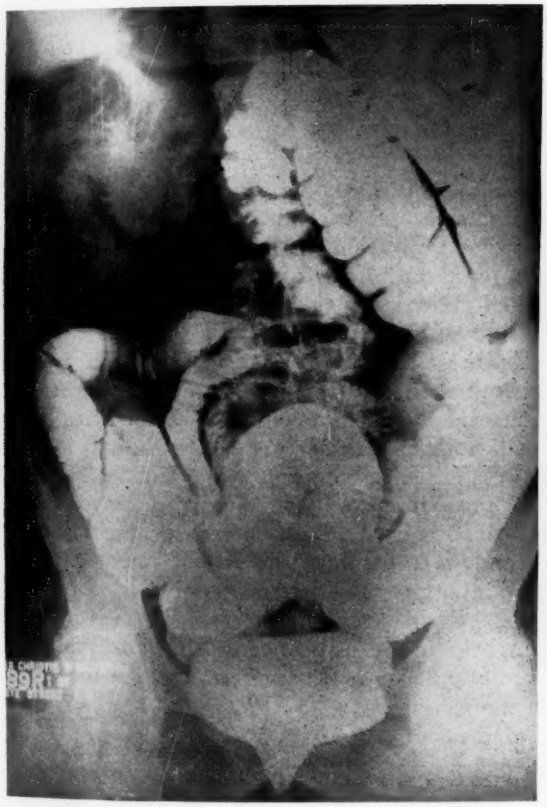

FIGURE 4. *Follow-Up Roentgenogram Thirteen Months after Operation, Showing Barium Filling the Distal Half of the Colon and Ileum and Demonstrating the Ileotransverse Colostomy.*

there is a definite twist in the right half of the transverse colon, which overlies the fourth lumbar disk. There is a redundant loop of transverse colon in the left upper quadrant. Postevacuation films show the cecum to lie near the center of the true pelvis, indicating 180° of mobility — that is, from the right of the first lumbar vertebra counterclockwise to the midline in the true pelvis. The twist of the transverse colon disappears when the cecum is empty and in the true pelvis. The point of twist, or volvulus, in the transverse colon remains contracted, as though irritated by this mechanical action. Examination of the esophagus, stomach and duodenum is negative except that the stomach is displaced by a redundant loop of transverse colon, which lies lateral and crossed posterior to the stomach. After 24 hours the transverse colon has almost emptied itself so that the cecum is not visualized at this time. There is believed to be definite evidence of a twist, or volvulus, in the transverse colon that is apparently due to an unusually mobile cecum and ascending colon, simulating the congenital anomaly of failure of descent and rotation of the cecum.

On the basis of these findings operation was advised. The patient was prepared for operation by the use of Sulfathalidine, 1 gm. by mouth every 3 hours for 5 days, in addition to daily intravenous administration of protein hydrolysate, 5 per cent dextrose in physiologic saline solution, with added components of the vitamin B complex and ascorbic acid for 4 days prior to operation.

The preoperative diagnosis was "Recurrent volvulus of the transverse colon probably due to a congenital anomaly of mobile cecum and ascending colon." At operation* the abdomen was opened through a right-rectus-muscle-splitting incision. When the peritoneal cavity was opened the cecum was not visualized. The transverse colon was seen, and it was noted that the cecum was in the true pelvis. When the cecum was delivered out of the pelvis there was an opening in the mesentery of the small gut 15 cm. from the ileocecal region. The cecum, ascending colon and terminal 30 cm. of the ileum had herniated through the 8-cm. opening in the small-bowel mesentery. The cecum was completely covered with peritoneum, and so was the ascending colon.

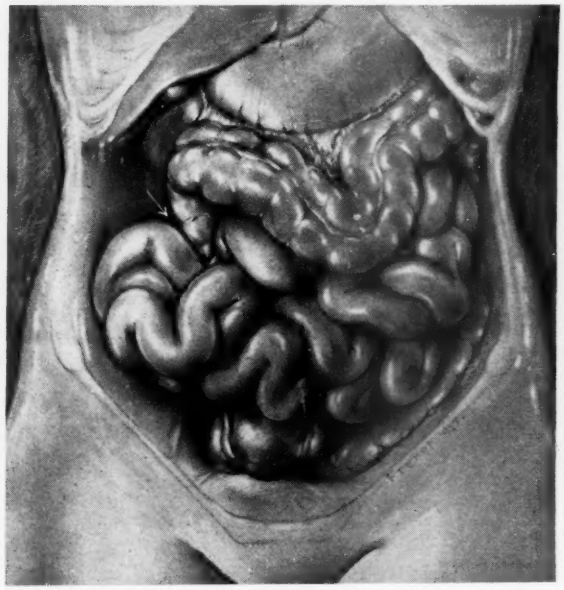

FIGURE 5. *Drawing Representing Findings at Operation and Showing the Freely Mobile Right Colon and Terminal Ileum Herniated through the Hiatus (Arrows) in the Mesentery of the Small Bowel.* (*Courtesy of Dr. J. William Hinton, of New York City.*)

Note the cecum lying in the true pelvis.

In view of that, it was thought best to resect the terminal ileum, cecum and ascending colon and do an end-to-side anastomosis that would eliminate any possible herniation in the mesentery. The terminal 30 cm. of the ileum, cecum and ascending colon were completely mobilized, the blood supply divided, and an end-to-side anastomosis done between the terminal ileum and the right half of the transverse colon over a Furness clamp. The proximal end of the transverse colon was closed with two layers of interrupted No. 3 cotton sutures, and then the anastomosis between the ileum and transverse colon was accomplished with 2 layers of interrupted No. 3 cotton sutures. When the anastomosis was done, the opening was patent, admitting the

*Performed by Dr. J. William Hinton, of New York City.

insertion of the index finger. There was no redundant end of the transverse colon. The closed end was flush with the anastomosis between the ileum and transverse colon. The

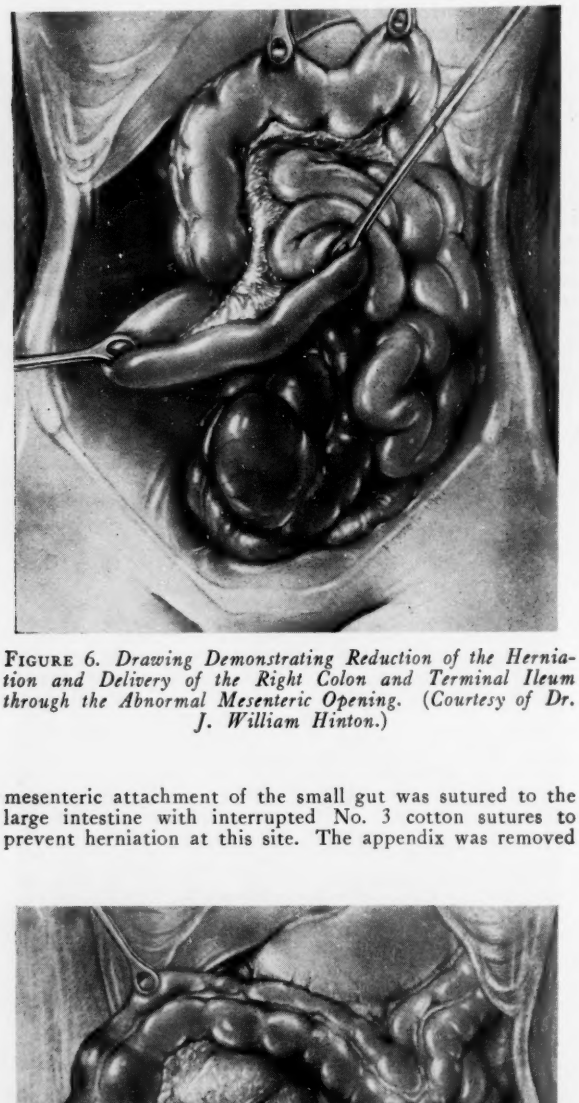

FIGURE 6. *Drawing Demonstrating Reduction of the Herniation and Delivery of the Right Colon and Terminal Ileum through the Abnormal Mesenteric Opening.* (*Courtesy of Dr. J. William Hinton.*)

mesenteric attachment of the small gut was sutured to the large intestine with interrupted No. 3 cotton sutures to prevent herniation at this site. The appendix was removed

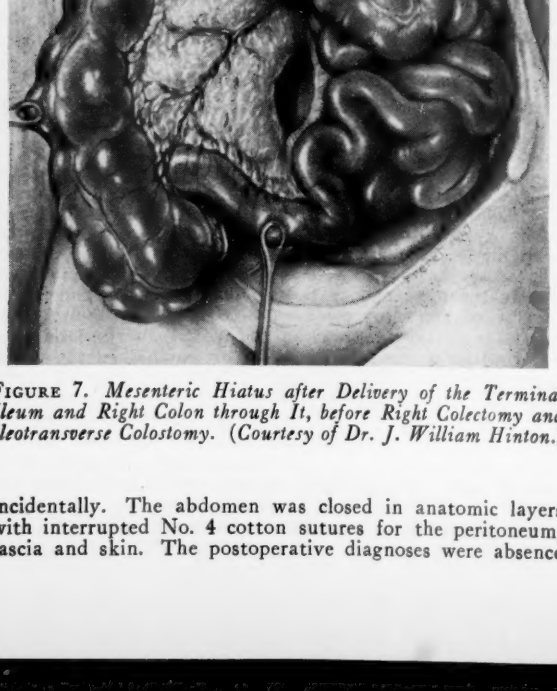

FIGURE 7. *Mesenteric Hiatus after Delivery of the Terminal Ileum and Right Colon through It, before Right Colectomy and Ileotransverse Colostomy.* (*Courtesy of Dr. J. William Hinton.*)

incidentally. The abdomen was closed in anatomic layers with interrupted No. 4 cotton sutures for the peritoneum, fascia and skin. The postoperative diagnoses were absence of the mesocolon of ascending colon (mobile cecum), torsion of the ileocolon and chronic obliterative appendicitis (Fig. 5-7).

The postoperative course was uneventful, and the patient left the hospital on the 19th postoperative day. During this period and for an additional 2 weeks she experienced a diminishing amount of diarrhea, with frequent, soft, formed stools. Follow-up study at frequent intervals for 37 months indicated normal health and entire absence of any further diarrhea and no abdominal symptoms whatever. The follow-up barium-enema examination, done 13 months after operation, is shown in Figure 4.

An anomaly of the colon resulting in periodic volvulus over a period of many years was identified by barium enema. Numerous previous x-ray examinations by competent radiologists had been negative. In all probability the diagnosis was not made because of *failure to take spot films of the point of torsion of the transverse colon during fluoroscopy and also because the examination of the colon did not include postevacuation films.* At operation the anomaly was found to consist of a freely movable, right half of the colon, completely covered with peritoneum and without mesenteric attachments, allowing a rotation of the cecum, ascending colon and terminal 30 cm. of the ileum, which had herniated periodically through an 8-cm. opening in the small-bowel mesentery.

At the time of the abnormal rotation a torsion at both the terminal ileum and the midpoint of the transverse colon had resulted, with a hiatus in the small-bowel mesentery through which loops of bowel periodically became strangulated. The operative procedure consisted of a resection of the terminal 30 cm. of ileum, the mobile cecum and the ascending colon, with the establishment of an end-to-side anastomosis of the terminal ileum and the right half of the transverse colon. This procedure thus eliminated any possibility of rotation or of herniation of bowel segments through the opening in the mesentery.

CASE 2. An 89-year-old, twice-widowed woman was seen on January 13, 1948, complaining of generalized abdominal pain for 5 hours' duration. The pain was sudden in onset, unlike any previous pain, and was accompanied by nausea and retching but without the vomiting of food. There had been a normal bowel movement that morning and no diarrhea. Flatus was normally passed without difficulty, but there had been none since the onset of the pain, which was crampy, colicky and generalized but most intense in the umbilical region and severe enough to cause the patient to cry out. There had been no change in bowel habits and no laxatives had ever been needed. She had never been operated on. There was no history suggesting gall-bladder disease or renal colic. A review of the systems was otherwise negative.

She had had the usual childhood diseases. At the age of 3, she had gone in a covered wagon from Ohio to Colorado. Two years later she had had "black" measles. She had been married at the age of 21 and had had 2 pregnancies, with 2 living children. One of these was living and well, at the age of 62. The other had died at the age of 59 of carcinoma of the ovary. At the age of 79, the patient had had pneumonia, followed by a complete recovery. There have been no operations and no injuries and no previous attacks similar to the present illness. The family history was otherwise irrelevant.

Physical examination revealed a well preserved, alert woman in marked distress, who appeared acutely ill. The structures of the head and neck were not remarkable. The heart was enlarged to percussion, with the apex 10.5 cm. to the left of the midline in the 5th intercostal space. There

was a to-and-fro systolic and diastolic murmur, heard over the entire precordium, loudest in the aortic region. The lungs showed a few crepitant rales at each base. The abdomen was moderately distended and tender generally without localization. There was no muscle spasm or rigidity, and no masses or organs were felt. Peristalsis was high pitched, gurgling and tinkling. Pelvic and rectal examinations were negative. There was a very slight edema of both ankles, most marked on the left.

The temperature was 98.0°F., the pulse 108, and the respirations 20. The blood pressure was 210/110.

Urinalysis was negative except for a faint trace of albumin. Examination of the blood showed a red-cell count of 3,110,000 with a hemoglobin of 11.5 gm. per 100 cc. (75 per cent) and a white-cell count of 7850, with 64 per cent neutrophils, 4 per cent eosinophils and 32 per cent lymphocytes. No x-ray examination was done.

The patient was prepared for an immediate operation,* 9 hours after the onset of the attack. The preoperative diagnosis was either acute intestinal obstruction due to neoplasm or ileus secondary to mesenteric thrombosis, in addition to arteriosclerotic heart disease, with aortic calcific stenosis and regurgitation, questionable mild congestive heart failure and senility. The anesthetic was Pentothal Sodium given intravenously, followed by ethylene and oxygen in addition to local intercostal block with novocain.

A right-rectus-muscle incision was made. When the peritoneum was opened a large quantity of serosanguineous fluid escaped from the abdominal cavity. Exploration of the abdomen revealed a band that had strangulated about 40 to 45 cm. of small bowel in the midileum. The bowel and mesentery were dull purple. Shortly after the band was cut the color became strawberry red. It bled slightly from the congested surfaces, but after a short time the bowel seemed to have fairly good circulation. Pulsations could be felt in the small mesenteric vessels close to the intestinal wall. Because of the patient's age it was considered safest not to do a resection. Further exploration did not reveal any abnormality. The abdomen was then closed in layers without drainage. When the patient left the operating table her condition was fairly good. The postoperative diagnosis was acute intestinal obstruction of the small bowel from "congenital bands."

The postoperative course was remarkably uneventful. The temperature did not exceed 100.2.°F. On the 2nd day normal peristalsis had returned. On the 3rd day the patient passed a small amount of flatus and had a small liquid stool. She was out of bed on the 2nd postoperative day and ready for discharge from the hospital at the end of 1 week. Follow-up study at the end of 24 months showed the patient to be in normal health, with no abdominal symptoms. She was active, doing all her own housework and going out frequently.

In this elderly woman, the symptoms and signs of acute intestinal obstruction were clearly present. Before operation it was believed that a previously silent neoplasm of the bowel or a mesenteric thrombosis was the most likely etiology. Despite doubt of the wisdom of operation because of her advanced age and of the complicating arteriosclerotic heart disease, the decision was made to explore the abdomen. On inspection the segment of gangrenous ileum was readily apparent, though the congenital band constricting the blood supply at the base of the mesentery was less easy to identify. After release of the constricting band, the previously absent pulsations in the arterial supply promptly returned, and the dark reddish-black bowel of questionable viability was not resected. It was believed that the patient would not tolerate such a procedure, and there was serious doubt, in any event, of her recovery. The postoperative course, however, was completely uneventful, with no complication whatever.

Three features in this case are worthy of special emphasis: An unexpected lesion was produced by a congenital band at an age when such a condition is rarely seen. After release of the band, a seriously damaged bowel segment, whose viability was highly questionable, recovered without resection. Operation was well tolerated at the age of eighty-nine in the presence of complicating heart disease.

*Performed by Dr. Richard Jackson, of Washington, D. C.

Summary

Two cases of congenital anomalies of the digestive tract in middle life and old age are reported. The literature on the subject is briefly reviewed.

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THERAPEUTIC EXPERIENCES WITH SUBACUTE BACTERIAL ENDOCARDITIS*

With Special Reference to the Failures

DAVID LITTMANN, M.D.,† AND ROYAL S. SCHAAF, M.D.‡

BOSTON AND WEST ROXBURY, MASSACHUSETTS

SUBACUTE bacterial endocarditis, until recently an almost uniformly fatal disease, now carries a mortality not unlike that of untreated bacterial pneumonia, about 30 per cent. Reports during the past five or six years have stressed the uniformly striking results achieved through the use of antibiotics. One such paper[1] emanating from the Massachusetts General Hospital related the experiences at that institution during the three-year period 1944–1946. Forty-four patients were treated, and of these 29 recovered,§ an incidence of 66 per cent. Actually, 6 of the failures should properly have been omitted from the series in that the patients received wholly inadequate quantities of penicillin. These people died essentially untreated and when deleted from the study alter the recovery rate to 76 per cent, which is in substantial agreement with that in other contemporary reports.[2, 3]

Recently, we reviewed the therapeutic results in subacute bacterial endocarditis at the Massachusetts General Hospital and the West Roxbury Veterans Administration Hospital for the years 1947-1949. We were impressed by the increasing infrequency of the disease but also by the unexpectedly high death rate despite what by present standards constituted adequate and in many cases more than adequate treatment. By adequate treatment is meant the use of such quantities of the appropriate antibacterial agent or agents as are indicated after identification of the organism and determination of its sensitivity to available antibiotics. In practice this amounted to the administration of from 1,000,000 to 30,000,000 units of penicillin a day for thirty to sixty days. Most patients received 1,000,000 or 2,000,000 units per day (by intermittent intramuscular injection) for thirty days, although 500,000 units a day is probably sufficient in most cases.[3] When no organism could be demonstrated the dosage was generally about 2,500,000 units a day for a month. Streptomycin and, more recently, aureomycin were employed in a few cases. Anticoagulants were not used.

The dosage levels were greater and the variety of drugs employed superior to those available during the 1944-1946 period. In spite of this, the recovery rate in 37 adequately treated patients with subacute bacterial endocarditis was only 62 per cent, in contrast to 76 per cent in the earlier period.

In the years 1947-1949 at the Massachusetts General Hospital there were 38 patients with bacterial endocarditis. Of these 6 were acute cases, all of which were fatal. Notwithstanding better diagnostic and therapeutic methods and occasionally reported cures,[4] acute bacterial endocarditis remains an exceedingly serious disease. Enormous quantities of antibiotics were administered in several cases without significantly influencing the course of the illness. As this paper is primarily concerned with endocarditis lenta these cases will not be further considered. Of the remaining 32 cases of bacterial endocarditis 5 were discovered at autopsy or immediately ante mortem and too late for any significant therapy. Two of these were marantic or terminal complications of other fatal illnesses. The other 3 patients had outright subacute bacterial endocarditis and died untreated because the diagnosis was overlooked. These 5 patients are not being considered with the treated cases but are included in the determination of gross incidence. Of the original 38 cases of bacterial endocarditis, therefore, 30 were considered to be clinical subacute bacterial endocarditis. These were collected out of admissions totaling 50,666, an incidence of 0.59:1000 admissions. During the previous three-year period at the same institution there were 51 similar cases out of 46,601 admissions, an incidence of 1.12:1000. It appears, therefore, that at the Massachusetts General Hospital the incidence of subacute endocarditis has diminished by almost half (Table 1).

TABLE 1. *Incidence of Subacute Bacterial Endocarditis at the Massachusetts General Hospital.*

PERIOD	TOTAL ADMISSIONS*	CASES OF CLINICAL SUBACUTE BACTERIAL ENDOCARDITIS	INCIDENCE PER THOUSAND ADMISSIONS
1944-1946	46,601	51	1.12
1947-1949	50,666	30	0.59

*Includes Massachusetts General Hospital, Baker Memorial and Phillips House.

*From the Medical Services of the Massachusetts General Hospital and the West Roxbury Veterans Administration Hospital.

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†Instructor in medicine, Tufts College Medical School; cardiologist, Veterans Administration Hospital, West Roxbury, Massachusetts; clinical fellow in medicine, Massachusetts General Hospital.

‡Teaching assistant in medicine, Harvard Medical School; research and clinical fellow in medicine, Massachusetts General Hospital; trainee, National Heart Institute.

§No patient was considered well who had not remained symptom free for at least six months.

During the same three-year period at the West Roxbury Veterans Administration Hospital there were 10 patients with subacute endocarditis. All were adequately treated according to the foregoing definition, and of these, 6 recovered. These cases have been combined with those from the Massachusetts General Hospital for the entire six-year period. Altogether there were 52 recoveries and, despite adequate treatment, 23 deaths. The failures have been combined for purposes of analysis and for comparison with the cases in which the patients recovered. It is hoped that useful features of prognosis or treatment may become apparent through such a review. A summary of the adequately treated cases of subacute bacterial endocarditis is given in Table 2.

TABLE 2. *Results in 75 Adequately Treated Cases.*

SOURCE	RECOVERIES		DEATHS	
	NO.	PERCENTAGE	NO.	PERCENTAGE
Massachusetts General Hospital (1944-46)	29	76.3	9	23.7
Massachusetts General Hospital (1947-49)	17	62.1	10	37.9
West Roxbury Veterans Administration Hospital (1947-49)	6		4	
Totals	52		23	

The following categories were considered: age and sex; duration of symptoms before institution of therapy; bacteriology; treatment (antibiotics employed and total dosage and duration of therapy); nutritional status of the patient; cardiac status (valvular lesion, congenital lesion if present, cardiac enlargement, cardiac decompensation and arrhythmias; renal status; and cause of death.

AGE

There was a striking similarity in the mean age of the patients who recovered as compared to those who died, forty years in the former and forty and six tenths in the latter. The youngest patient who recovered was three and a half, and the oldest seventy-three years old. The youngest patient who died was seventeen, and the oldest sixty-seven. Age, apparently, was unrelated to the eventual outcome of the disease.

SEX

There was no significant difference in sex distribution between the two groups.

DURATION OF ILLNESS BEFORE RECOGNITION

Delay in diagnosis did not often make the difference between recovery and failure. In the cases in which it did, however, it was of vital importance. In the 3 patients mentioned earlier the diagnosis was not made before death or too late in the course of the disease for adequate therapy to be instituted. In the treated patients the average duration of symptoms before therapy was eleven and six-tenths weeks in those who died as against ten and seven tenths in the cured cases. In a patient who recovered, nine months elapsed before treatment was begun. In a fatal case that was never treated symptoms had apparently been present for almost ten months. However, in another patient, who died as the result of irreversible cardiac failure and embolic nephritis, treatment with penicillin was carried out at home for only one month (presumably in ignorance of the correct diagnosis), and the patient gradually succumbed to the effects of *Haemophilus influenzae*; the organism in this case was belatedly controlled with streptomycin.

BACTERIOLOGY

No significant difference was noted in the bacteriology of the two groups. Alpha-hemolytic streptococcus was the predominant organism, but the gamma type occurred occasionally. Four patients with infections due to *Staphylococcus albus*, 1 with infection due to a beta-hemolytic streptococcus, 1 with infection due to *Streptococcus faecalis* and 2 with infection due to *H. influenzae* recovered.[5] Eight patients with endocarditis caused by alpha-hemolytic and gamma-hemolytic streptococcus and 1 with infection due to alpha-hemolytic, beta-hemolytic and gamma-hemolytic streptococcus also recovered. *Staph. aureus* was encountered only in the cases of acute endocarditis. Paul and his associates[1] concluded that in 6 of their cases regarded as failures the patients died with uncontrolled infections. However, 2 of these were essentially untreated. Of the remainder, 2 died with active infections in spite of massive doses of penicillin. In the 1947-1949 group 2 additional cases were observed who had resistant organisms. Of these refractory bacteria, 2 were alpha-hemolytic and the other 2 gamma-hemolytic streptococcus. Heroic doses of antibiotics were employed in all 4 cases. Resistance to the medications employed was not observed in any case.

ANTIBIOTICS

All patients were treated with penicillin, and some received streptomycin in addition. Sulfadiazine was used in a few cases, and aureomycin in 2. The dosage of penicillin varied; in general, the largest amounts of the drug were given to the sickest patients, including those who died. It is worthy of note that with one exception (301,000,000 units given before death) the average total dose of penicillin in Paul's well treated cases regarded as therapeutic failures was 35,000,000 units. In the subsequent three-year period the patients in whom therapy was considered a failure received an average dose of 80,000,000 units. Those who recovered averaged 60,000,000 units. The largest total dose was 516,000,000 units combined with 38 gm. of

streptomycin. This resulted in a cure in a patient with a resistant *Staph. albus* infection. The largest daily dose was 30,000,000 units.

Nutritional Status

The nutritional state reflected the degree of illness and, as expected, was worst in the sickest patients. Of those who died 49 per cent were poorly nourished, and 20 per cent fairly well nourished, and only 31 per cent were well nourished. Among those who recovered only 6 per cent were poorly nourished, and 31 per cent were fairly well and 63 per cent well nourished.

Cardiac Status

In all patients of this group subacute bacterial endocarditis was, as far as could be determined, superimposed on pre-existing valvular or congenital heart disease, or both. The valvular changes were almost exclusively rheumatic. Two patients were considered to have clinical evidence of calcareous aortic stenosis. Syphilitic heart disease was not seen, although positive blood serologic findings were encountered in 2 cases.

Congenital heart defects were present in 5 patients who died, an incidence of 22 per cent, and in 5 who lived, an incidence of 9 per cent. One lesion, congenital bicuspid aortic valve, was found in 4 cases at autopsy. It was suspected in a patient who also had a patent ductus arteriosus; this patient recovered. Tetralogy of Fallot was encountered in a patient who lived and in another who did not. Two patients with ventricular septal defects and 1 with pulmonary stenosis recovered. The surprising frequency of bacterial endocarditis on bicuspid aortic valves confirmed earlier observations[6] that this defect is peculiarly vulnerable to infection. The combination, however, turned out to be more malignant than was anticipated. Curiously enough, despite the reported frequency of subacute endocarditis in coarctation of the aorta[7] this lesion was not encountered at all in the 75 well treated cases, 16 undertreated or unrecognized cases and 6 patients with acute bacterial endocarditis.

Except for congenital defects, the type and frequency of the valvular lesion were similar for the two groups. Changes in the mitral and aortic valves were found together in a third of all the cases. Pure mitral stenosis was the rarest abnormality and was seen only once in the entire series.

Cardiac Arrhythmias

Auricular fibrillation was present with about equal frequency in the two groups. It occurred in chronic or transient form in 11 patients. Paroxysmal auricular tachycardia was noted briefly in a patient who subsequently recovered.

Cardiac Enlargement

Evidence of cardiomegaly on x-ray examination proved to be a useful prognostic sign. The presence of significant enlargement was found in 71 per cent of the fatal cases and in 47 per cent of the patients who were cured.

Cardiac Failure

A rather more impressive difference was seen in the relative incidence of myocardial insufficiency. Evidence of frank failure was apparent at some time during the course of the illness in 75 per cent of the unsuccessful cases. Minor decompensation occurred in another 9 per cent, and no failure was present in the remaining 16 per cent. By contrast, obvious failure occurred in only 13 per cent of the cured cases, and lesser degrees of decompensation in another 4 per cent. This single manifestation most nearly paralleled the final results, and its presence generally indicated an unfavorable prognosis.

Renal Status

Renal failure, the result of embolic nephritis, was seen in 3 fatal cases. It was the sole cause of death in 1 patient but occurred together with congestive heart failure in the other 2. Significant nitrogen retention was not encountered in the patients who recovered.

Table 3. *Cause of Death in 23 Adequately Treated Cases.**

Cause	No. of Cases
Congestive heart failure	10
Congestive heart failure and uremia	2
Congestive heart failure and cerebrovascular accident	1
Cerebrovascular accident	4
Uremia	1
Pulmonary embolism†	2
Ruptured splenic abscess	1
Cause unknown‡	2
Total	23

*Of the patients listed 4 died away from the hospital and were not examined post mortem. No permission for autopsy was obtained in 2 others. The remainder were all studied post mortem.

†Permission for autopsy not obtained.

‡Patients died outside hospital.

The causes of death in 23 adequately treated cases of subacute bacterial endocarditis are summarized in Table 3.

Discussion

It is evident from a review of the categories just considered that the age and sex of patients with subacute bacterial endocarditis were unrelated to the final outcome. Lack of awareness and of early recognition of the diagnosis was of supreme importance to a few patients who succumbed essentially without treatment. In the remainder,

however, the average elapsed time before the institution of therapy was similar for the two groups. The presence of a completely resistant organism inevitably resulted in failure but was fortunately uncommon. It should become even more so in the face of the more diverse antibiotic agents now available and the larger doses employed. Except in those cases, persistent infection at death was due to treatment administered either too late or in insufficient amounts. These patients died of phenomena related to the active infection such as cerebrovascular accident and splenic rupture. Early recognition and prompt, effective therapy should reduce the incidence of such mishaps and better the results in this group of patients.

As might be expected, the nutritional status mirrored the degree of illness and was consequently of distinct prognostic worth. Poor nutrition, other factors being equal, suggested an unsuccessful termination. Similarly, renal failure proved to be an ominous finding and was seen only in the patients who died. Uremia was encountered in 3 cases and was due in each to embolic nephritis. Two of the patients, however, also had congestive heart failure. A careful evaluation of the cardiac status was often the best clue to the eventual outcome. Congestive failure was rarely seen during the course of bacterial endocarditis in the patients who recovered. By contrast, 13 of the 23 patients who succumbed were in congestive failure terminally, and 10 died solely as the result of irreversible decompensation. In some cases this took place as long as six months after completion of therapy. Occasionally, patients with extensive valvular disease who survived for longer periods — especially those with aortic-valve insufficiency — became cardiac cripples with greatly limited reserves.* This was not invariably true, however. Other reports[8] have indicated relatively little alteration of cardiac status resulting from subacute bacterial endocarditis. Cardiac arrhythmias, although a good deal more frequent than commonly supposed,[9] were of no great prognostic significance.

In general, *the highest mortality from subacute bacterial endocarditis was seen in the patients with the most serious heart disease*, particularly in those in whom congestive failure occurred. This could sometimes be predicted when cardiac enlargement was present. Extensive aortic disease due to a congenitally defective (bicuspid) aortic valve appeared to be associated with an especially high mortality.

Seventeen patients who succumbed to subacute bacterial endocarditis died of the effects of infections that had themselves been successfully eradicated. In many of these cases irreversible and eventually fatal changes had taken place before treatment was begun. The outcome could not have been altered by late though normally effective therapy. Such patients could be cured only by earlier and still earlier institution of treatment, at a time preceding the development of intolerable structural alterations. Unfortunately, this period may also antedate the time when positive blood cultures can be obtained and hence the time when definite diagnosis can be made. It may yet prove desirable, therefore, to begin active antibiotic measures in all patients with known valvular or congenital heart disease who develop fever from *any cause*. Such a program would reduce the number of positive cultures and proved diagnoses but, on the other hand, might well diminish the total number of deaths from subacute endocarditis.

That such a prophylactic and therapeutic trend has already occurred is suggested by the lowered incidence of subacute bacterial endocarditis at the Massachusetts General Hospital. To be sure, it is unsafe to attempt a general interpretation and application of statistical events noted in one institution. Nevertheless, the striking diminution in the frequency of subacute bacterial endocarditis at this hospital merits an attempt at explanation. The reduction in the number of patients with endocarditis lenta by almost a half may merely indicate that more patients with this illness are being successfully treated at local hospitals or at home. It appears improbable, however, that patients *known* to have bacterial endocarditis are ever treated at home, even in this antibiotic age. More likely, unsuspected and probably undiagnosable cases are being cured by relatively brief courses of penicillin administered early for other suspected illnesses. The drug may be given at home or even on an ambulatory basis before endocardial infection gains a significant foothold. Such cases, to escape further notice and diagnosis, must, of course, be rather mild and easily cured. Support for this contention is afforded by the results of therapy in some of the early penicillin reports. For example, the series of Paul et al.[1] included cures obtained with 2,700,000 units of penicillin in fifteen days, 200,000 units a day for three weeks, and the like. Conversely, the patients who currently progress to clinical bacterial endocarditis despite early antibacterial treatment for other suspected maladies are apt to have more structural disease or more resistant organisms. Consequently, they are less likely to be cured even with adequate or massive treatment. The lowered recovery rate noted earlier in this report may well result from this preselection of the cases that eventually reach a metropolitan hospital. Yet another possible explanation for the lessened incidence of subacute bacterial endocarditis is more effective prophylaxis incident to dental extractions and surgical procedures.

Summary and Conclusions

Experiences with subacute bacterial endocarditis for the years 1947-1949 were collected and com-

*Since this paper was submitted two additional cured cases have died of irreversible failure associated with free aortic insufficiency.

pared with those for the preceding three years. The adequately treated failures, numbering 23 cases, were separately compared with the 52 recoveries.

Early recognition and adequate antibiotic therapy were important in obtaining cures and limiting permanent structural damage.

Most deaths (17 of 23) occurred as a consequence of irreversible cardiac, renal or cerebral changes despite sterilization of the blood stream. Infection was present terminally in only 6 cases, and 4 of these were considered due to truly resistant organisms.

The nutritional state of the patients was found to be of prognostic value. In approximately half the failures the patients were poorly nourished, and only 6 per cent of the cured patients were so designated.

Uremia and congestive failure were ominous events during the course of subacute bacterial endocarditis and commonly foreshadowed an unsuccessful termination.

Patients with the most serious heart disease fared the least well. There was a relatively high incidence of congenitally bicuspid aortic valves among those who died.

Although more resistant to therapy, subacute bacterial endocarditis was found to be less frequent (by almost 50 per cent) in recent than in former years. The reduction in total numbers was thought to be due in part to the currently widespread and probably justified use of antibiotics in patients with valvular heart disease for diagnoses other than bacterial endocarditis.

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FEBRILE THROMBOPENIC PURPURA WITH HEMOLYTIC ANEMIA AND PLATELET THROMBOSIS

Philip T. Goldenberg, M.D.,* John E. Thayer, M.D.,† and Louis P. Hastings, M.D.‡

Newington and Hartford, Connecticut

A CLINICAL syndrome characterized by fever, a rapidly progressing anemia, mild icterus, thrombopenia, central-nervous-system manifestations and death in a relatively short time was first described by Moschcowitz[1] in 1925. Since that time a limited number of cases that seemed to fit this picture clinically and pathologically in remarkable similarity have appeared in the literature, the outstanding features at autopsy having been the numerous petechial hemorrhages found in the heart, kidneys, liver and brain, which microscopical examination revealed to be due to platelet thrombi. As yet, no definite reason has been given to explain this peculiar sequence of events, which, in all likelihood, is initiated by a spontaneous deposition of the blood platelets owing either to an upset in the coagulating mechanism of the circulating blood or a preceding capillary and arteriolar injury.

We report below another case of this type in which the psychiatric manifestations were so prominent that the patient was at first believed to be suffering from a major psychosis and consequently was placed in a mental institution.

*Junior assistant resident in medicine, Newington Veterans Administration Hospital; formerly, resident in pathology, St. Francis Hospital, Hartford.

†Assistant pathologist, St. Francis Hospital.

‡Pathologist, St. Francis Hospital.

Case Report

A 23-year-old single woman was admitted to a mental institution on February 20, 1947, for treatment of a mental depression. About 5 weeks prior to entry she had begun to feel depressed and to experience severe headaches. She continued to work but, noting no improvement and a gradual sensation of "numbness all over her body" had decided to leave her job as a typist. Her symptoms progressed, and 2 weeks later she was found in bed, gazing into space and repeating that she felt ill. She did not answer questions and shortly thereafter became entirely mute. Five days before entry, a profuse vaginal flow started, although the last menstrual period had ceased only 5 days previously. Her physician was called and in view of her abnormal behavior admission to a mental hospital was advised.

The patient had always enjoyed good health and except for a minor surgical operation on one eye had been free of illness. There was no history of alcoholism or drug ingestion. The menses had been regular except for a missed period 3 months previously.

The family history was negative for nervous, mental, allergic and blood diseases.

Physical examination on admission to the first hospital revealed a well developed, fairly well nourished, drowsy woman with a clear, pale skin. The head was of normal configuration. The pupils were round and equal and reacted to light. The conjunctivas were pale; no petechiae were noted. Funduscopic examination was not carried out because of the patient's resistance. The buccal mucosa was pale. The

gums were in good condition, and no bleeding was noted. There was no cervical adenopathy, nor was the thyroid gland palpable. The breasts were normal. The chest was symmetrical and clear to percussion and auscultation. Examination of the heart revealed no abnormalities. The abdomen was normal, and no organs were palpated. Examination of the uterus and adnexa was negative but was considered unsatisfactory owing to the resistance of the patient. The axillary and inguinal lymph nodes were not palpable. The reflexes were normal throughout.

The temperature was 101°F., the pulse 100, and the respirations 22. The blood pressure was 100/70.

Examination of the blood showed a red-cell count of 2,070,000, with a hemoglobin of 36 per cent, and a white-cell count of 13,800, with 72 per cent neutrophils and 28 per cent lymphocytes.

During the next 6 days, the vaginal bleeding persisted, and in spite of repeated blood transfusions of Type A, Rh+ blood, the red-cell count rose only to 2,360,000 and the hemoglobin to 49 per cent, the differential count remaining unchanged. A lumbar puncture taken during this period revealed 4 red blood cells and 6 white blood cells per cubic millimeter. The protein was 32.0 mg., and the sugar 57.0 mg. per 100 cc. The Wassermann and Mazzini reactions were negative. The urine had a specific gravity of 1.016, with occasional red and white cells in the sediment. Examination for sugar was negative, and there was a ++ test for albumin. X-ray study of the chest was negative. An electrocardiogram showed T wave in Lead 2 to be of unstable configuration, being at times well pronounced, flat, slightly inverted and diphasic. The T in Lead 3 was inverted. These findings were interpreted as related to an unsatisfactory blood supply to the heart musculature. The patient ran a consistently elevated temperature of 101 to 105°F. and because of failure

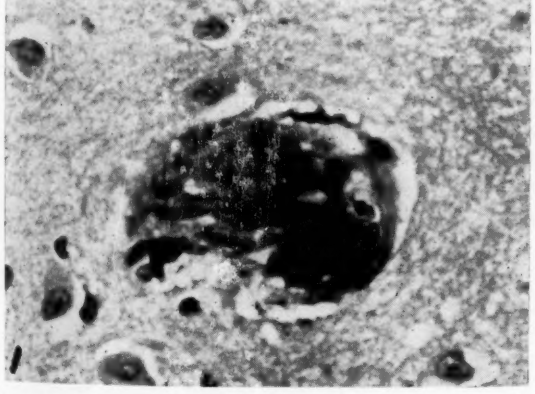

FIGURE 1. *Microscopical Appearance of the Cerebrum (x 300). Note the platelet thrombus in the vessel.*

to improve in spite of therapy was transferred to this hospital on February 27.

Physical examination on admission revealed a semicomatose woman, who did not respond to questioning and only slightly to intense stimulation. The skin showed numerous petechiae involving the arms and lower extremities, as well as signs of marked blood loss. The scleras were slightly icteric. Funduscopic examination revealed massive hemorrhages in the left disk and retina. There were also many small hemorrhages in the right retina. The chest appeared clear to percussion and auscultation. Examination of the heart demonstrated a sinus tachycardia and a Grade I apical systolic murmur. The liver was palpated two fingerbreadths below the costal margin. There was moderately profuse bleeding from the vagina. There were no palpable lymph nodes. Neurologic examination was negative. The remainder of the physical examination was unchanged.

The temperature was 103.2°F., the pulse 120, and the respirations 30. The blood pressure was 94/60.

Examination of the blood disclosed a red-cell count of 1,800,000, with a hemoglobin of 31 per cent and a white-cell count of 20,500, with 82 per cent neutrophils, 16 per cent lymphocytes and 2 per cent monocytes. Examination of the smear showed a + polychromatophilia, + stippling, +++ variation in size and shape and 11 erythroblasts per 100 white blood cells. The platelets were markedly decreased. The hematocrit was 16 per cent, the volume index 1.0, and the color index 0.8. No malaria organisms were seen. The prothrombin time was 60 per cent of normal, and the coagulation time 4 minutes. A tourniquet test was strongly positive. The stool was negative for occult blood. A blood culture taken on admission showed no growth in 72 hours. Urinalysis showed a specific gravity 1.016 to 1.020. The sugar reaction was consistently blue with a ++ to +++ test for albumin. The sediments were cloudy, with 1 or more white blood cells and 2 or 3 red blood cells per high-power field. The total

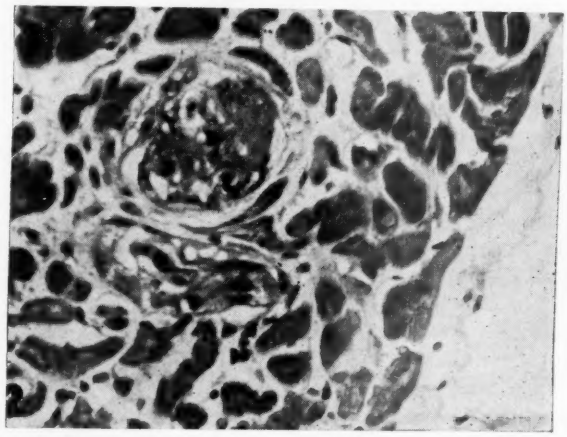

FIGURE 2. *Microscopical Appearance of the Heart (x 440). Note the platelet thrombi in the vessels of the heart, with marked endothelial swelling and proliferation.*

protein was 4.8 gm. per 100 cc., with 3.1 gm. of albumin and 1.7 gm. of globulin. The icteric index was 17.0.

A sternal-marrow biopsy revealed a scanty marrow take, with an erythroid myeloid ratio of 1:1.6. The myelogram was considered typical of severe secondary anemia, with a marked attempt at erythrocyte replacement suggestive of an excellent response to an anemia of sudden onset; megakaryocytes were slightly increased in number.

Treatment consisted of continuous transfusions of Type A, Rh+ whole blood, Reticulogen, penicillin, Amigen infusions and Ergotrate. The temperature continued to rise, and the patient's condition became more grave. The vaginal bleeding continued, and 16 hours before death it was noted that muscular twitchings of the face and a flaccid paralysis of the right leg had developed. Forty-eight hours after entry, the blood pressure could not be obtained, the pulse became imperceptible, and the patient died.

The clinical diagnosis was acute thrombopenic purpura, type and cause unknown.

At autopsy (4 hours after death) the body was that of a slightly icteric woman with no gross abnormalities except scattered petechiae and purpuric hemorrhages on the abdomen and all extremities. The heart weighed 300 gm. and was normal in consistence except for a slight doughy sensation to palpation. The epicardium was studded with petechial hemorrhages, especially at the base. All valves were normal, and there was no evidence of endocarditis. Cross sections through the myocardium of both the left and right sides of the heart showed it to be scattered with pin-point hemorrhages and punctate areas of yellowish necrosis. The coronary vessels were normal. The spleen was normal in size and weighed 100 gm. Its color was slightly darker than normal, and through the capsule could be seen three scattered pale

areas, which were approximately 2 to 5 mm. in diameter and represented superficial infarctions. The uterus was virginal in size, type and position, and no hemorrhages could be found in the endometrium. Both fallopian tubes were filled with blood, and a recent ruptured hemorrhagic follicle was noted in the right ovary. The vagina was ballooned with soft blood clots, which appeared to have originated in a slightly dilated cervical canal showing no evidence of instrumentation or primary disease. The brain was somewhat tense beneath the dura and markedly congested. The leptomeninges disclosed no meningeal reaction. Cross sections through the brain demonstrated many punctate hemorrhages

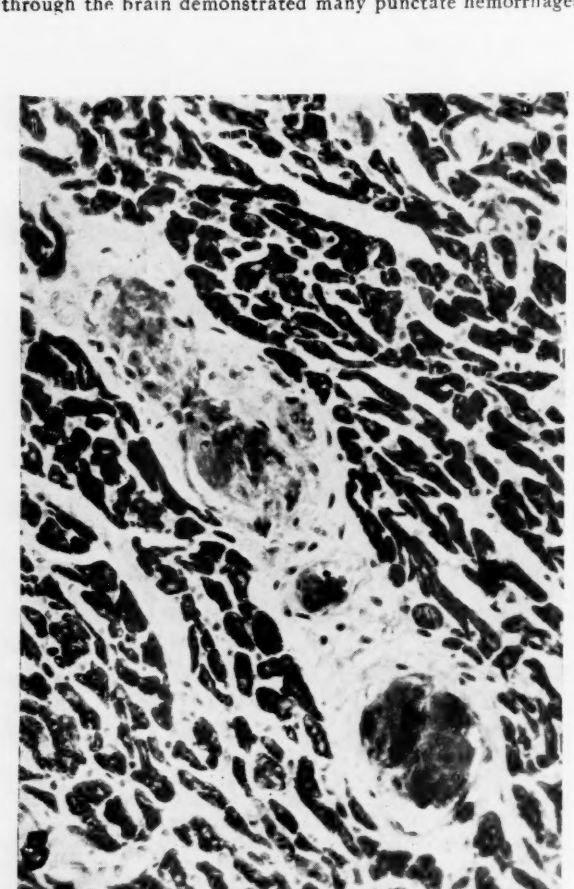

FIGURE 3. *Photomicrograph of a Section of the Heart (x 270). Note the platelet thrombi, illustrating varying stages of pathogenesis in a small area of tissue.*

in the gray matter of the cerebral cortex, substantia nigra of the cerebral peduncles and pons. The white matter of the cortex, basal ganglions and medulla showed no petechiae. The vessels at the base of the brain were soft and flexible, with no lesions or thrombi. Aside from passive congestion of the lungs and liver, no other abnormalities were noted.

On microscopical examination practically all organs are marked by thrombi in the smaller arterioles and capillaries. These failed to give a fibrin reaction with various stains* and had the characteristics of deposited and agglutinated platelets. The pathogenesis of these lesions apparently started with an embolic deposition of these platelets, exciting a swelling of the endothelium, which then proliferated over the thrombus forming a new endothelialized lumen. Later, the endothelium disappeared from beneath the thrombus, leaving it extraluminary. Rarely, a second thrombus was formed in these areas, and the process was repeated. Surprisingly enough, the embolic thrombi did not excite any cellular inflammatory response, nor was there evidence of organization of the older lesions. The cellular degeneration of parenchymal tissue was disproportionately less than the widespread vascular lesions. Examples of these thrombi may be seen in Figures 1, 2 and 3.

In the heart the myocardial fibers showed patchy, diffuse, anoxic degeneration, which was much less in extent than the vascular involvement led one to expect, unless most of the thrombi were very recent or did not completely obstruct the blood flow.

In the kidney, there were thrombi in afferent arterioles and in the glomerular tufts, and hyaline casts in the tubules but no inflammatory response in these regions.

Similar thrombi were found in the adrenal cortex accompanied by hemorrhage, in the portal areas of the liver, in the vessels of the marrow, which also showed a slight increase in megakaryocytes, in the posterior lobe of the pituitary body but not in the anterior lobe, and in the brain, where they had excited small perivascular hemorrhages of the anoxic type.

The anatomic diagnoses were capillary and arteriolar platelet thrombi of the heart, lungs, liver, spleen, kidneys, adrenal glands, cerebrum and bone marrow; focal necrosis of the myocardium and spleen; hyperplastic bone marrow; and severe anemia and bilirubinemia, with generalized icterus.

Discussion

The clinical and pathological findings described above are similar to those in previously reported cases. It is conceivable that the lesions in the brain could have accounted for the picture presented at the onset of the illness. Certainly, the neurologic findings noted terminally were on the basis of multiple platelet thrombi in the brain. The profuse and persistent vaginal bleeding further complicated the picture, and it was not until the appearance of the petechiae forty-eight hours before death that a blood dyscrasia was suspected. The associated appearance of a mild icterus and diminished platelets in the peripheral blood, with a prolonged bleeding time and positive tourniquet test, was further evidence in support of such a diagnosis. Nonetheless, a correct diagnosis could not be made in this case.

It was not until 1936, eleven years after Moschcowitz's[1] initial description that Baehr, Klemperer and Shifrin[2] reported 4 cases and further clarified the clinical and pathological findings. The hyaline thrombi previously noted by Moschcowitz were actually, according to these authors, depositions of platelets within the arterioles and capillaries of the involved vessels. Gitlow and Goldmark[3] reported a case in which the clinical and pathological findings were similar to these and stated that the condition is possibly related to periarteritis nodosa, the inflammatory reaction of the blood-vessel walls, characteristically absent in these cases, being explained on the basis that here was perhaps an acute type of periarteritis nodosa with death resulting before the real pathology of the latter disease developed. Recently, Engel, Scheinker and Humphrey[4] reported a case of this syndrome in which sensitivity of the patient to sulfathiazole and sulfadiazine was shown. They believed, however, that there

*Stains employed were hematoxylin and eosin, Masson's trichrome and phosphotungstic acid.

was no relation between the sensitivity manifestations and the syndrome under discussion.

In view of Rich's[5] work on the relation of sulfonamide sensitivity to the lesions of periarteritis nodosa, such an assumption may not easily be dismissed. However, in only 1 case has such a sensitivity been shown, and this cannot be taken as definite evidence. Furthermore, it is the opinion of most observers that the disease is not related histologically to periarteritis nodosa. The lack of degenerated collagen uniformly present in lupus erythematosus disseminata speaks against a relation of this syndrome to the former. Also, the thrombi in lupus erythematosus disseminata are not of the platelet type. Altschule[6] was of this opinion, believing that the disease belonged to the group of acute essential thrombocytopenias. Alice Bernheim,[7] in a case similar to the one under discussion, could not demonstrate the presence of agglutinins for platelets of the same blood group as her patient. She did show, however, areas of ischemic necrosis in the brain that accounted for the cerebral symptoms and death of the patient. Trobaugh et al.,[8] in 1946, reported the first case in a male. Subsequent reports[9-11] have shown 4 additional cases in males. In 1947 Fitzgerald[9] presented 3 cases and a complete review of the literature to that time. In his excellent summary, he also demonstrated by differential staining technics that the common components of vascular thrombi, such as leukocytes, collagen, fibrin (a small amount of this was present), hemoglobin and hemosiderin, were not found in the platelet thrombi. In the cases in which lesions have been observed in the lungs, groups of megakaryocytes occluding the small blood vessels were noted. Morphologically at least, it is the consensus that these thrombi are masses of precipitated platelets. Fitzgerald proposed that this syndrome be called "thrombotic acroangiothrombosis," a title that is well taken in view of the pathological findings in the terminal arterioles, capillaries and venules. Singer et al.[12] presented a case occurring in an eleven-year-old girl. These authors proposed the name "thrombotic thrombocytopenic purpura." Carter[10] described a case in a Negro in which fibrin threads were observed in the lumen of both involved and uninvolved vessels. In some of the vessels, platelets were noted adhering to these fibrin threads. This finding was not seen in the case reported above, nor was it previously observed. Its significance in the mechanical formation of the thrombi is appreciated, but why such a process is initiated is still not explained. Engel, Scheinker and Humphrey,[4] as mentioned above, described a case in which the administration of sulfonamides resulted in the appearance of chills, malaise, rise in temperature to 104.2°F., tachycardia (pulse of 140), leukocytosis (white-cell count of 19,150) and confusion, but no change in hemoglobin, red-cell count, urine or icteric index. The reaction cleared in twenty-four hours. The authors believed that the reaction played no etiologic role in their case. Nevertheless, it may be that the confusion seen in their patient after the administration of the sulfonamides was associated with an increased formation of platelet thrombi in the central nervous system. The patient was discharged fifty days after the onset of her illness but approximately two months later died with an acute exacerbation of her disease in spite of an emergency splenectomy. It is not meant to imply here that there was a direct relation between this syndrome and sensitivity to the sulfonamides, but rather that the administration of the drug may have aggravated the disease already present. Extensive neuropathological examination in this case revealed thrombotic occlusion of the capillaries and vessels of the cortical gray matter and basal ganglions. It is interesting also that these authors observed degenerative changes in the endothelial cells of the vessels, a finding not ordinarily seen. The dense glial reaction noted in the nervous tissue was attributed to healing and scar formation over the three months' course of the disease, longer than that of any of the other patients reported. Ehrich and Seifter[13] recently reported another case in which they attributed the development of the disease to an iodine-containing drug. Studies of the iodine content of the kidneys, liver, lungs and heart revealed these tissues to contain considerable amounts of iodine. The authors suggested that the purpura was the result of an antigen-antibody reaction involving the cells of the thrombocytic series. Green and Rosenthal[11] reported on 3 cases from the Mount Sinai Hospital, 1 of which had been previously described by Bernheim.[7] Use of the benzidine stain on their sections showed that the thrombi were not composed of red blood cells. Mental aberrations were noted in 2 of the cases and probably were related directly to the disease. The pathological findings were similar in all cases, and the surprising lack of parenchymatous degeneration associated with the platelet thrombi in the cerebral cortex was observed.

Another possibility to explain this phenomenon is suggested by the work of Copley and Robb[14] who first pointed out that commercial samples of heparin may actually cause agglutination of platelets in vivo and in vitro. This phenomenon is transient in these and other experiments, so that, although the platelet count may drop precipitously as the clumps of platelets are filtered out by the capillaries,[15] the thrombi disappear as the platelets return to the circulation undamaged. Whether a heparin-like substance with this property appears in the disease is not yet proved.

That the disease may be the result of varied factors is obvious from the case reports. Nonetheless, the similarity in the clinical and pathological findings points to an underlying mechanism that is basically the same in all — namely, precipitation of platelets

within the smaller arterioles and capillaries. Whether the initiating factor is an antigen-antibody reaction or a defect in the vascular endothelium cannot be stated.

Treatment for this condition has been useless thus far. Splenectomy was attempted in several cases but was followed shortly thereafter by death of the patient. Transfusions of whole blood are used to combat the anemia and shock, but this is only temporary. The successful management of these patients must await the determination of the exact etiology of the disease. In all probability, the solution lies in the complete understanding of the complex clotting mechanism of circulating blood that has been the basic pathologic upset in these cases. Awareness of the fact that varied neurologic findings may occur in disorders of this type may prevent errors in disposition of such patients as occurred initially in the case reported above.

Summary

A case of acute hemolytic anemia, purpura hemorrhagica, thrombocytopenia, mild icterus, central-nervous-system manifestations and platelet thromboses of the arterioles, capillaries and venules verified at autopsy is presented.

The clinical picture was similar in many respects to that in the previously reported cases, but, owing to the early onset of nervous system manifestations, it was at first believed the patient was suffering from a psychotic episode and she had consequently been placed in a mental institution.

A discussion of the literature is given. No statement regarding exact etiology can be made.

The successful treatment of this disease is still unknown.

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MEDICAL PROGRESS

HYPERTENSION

DOROTHEA LOOFBOUROW, M.D.,* AND ROBERT S. PALMER, M.D.†

BOSTON

PROGRESS in hypertension has not been reported in this section before, although certain forms of treatment have been discussed. It has been our endeavor to describe, in the first place, the general progress that has been made in the field and, secondly, the recent investigative work. To accomplish this we have organized the material as follows: general etiologic theories, recent investigative work, recent work in pathology, treatment, and the natural history and evolution of essential hypertension derived from follow-up studies.

ETIOLOGY

Progress in the knowledge of hypertension may be considered to have taken place in hundred-year cycles: Harvey discovered the circulation of the blood (1628), Hales established the existence of a pressure that gives rise to blood flow (1733), Bright observed the fact that the heart becomes enlarged in cases of nephritis (1827), and Goldblatt developed a new method of producing experimental hypertension in animals (1934).[1]

According to the followers of Bright, hypertension is almost always a renal disease.[2] Later nineteenth-century clinicians (Mahomed, 1874, and Allbutt, 1896), leaving the deadroom for the bedside, concluded that in continued arterial hypertension a disorder of function precedes renal and vascular organic change. In the early years of this century, Anrep (1912) established the broad concept of vasomotor tone and balance that led to Cannon's[3, 4] principles of homeostasis and to Selye's[5] presently influential theory of the general adaptation syndrome and the diseases of adaptation, including hypertension.

This introduction to the subject is not for the purpose of making a conventional bow to the history of medicine but rather for the purpose of pointing out that there is still an unresolved controversy: those who support the renal theory contend that all hypertension, including essential hypertension, is a renal disease, and the neurohumoral theorists suppose that essential hypertension is a disease, or a group of diseases, with continued arterial hypertension as one sign of its presence, that the sign may, and frequently does, precede recognizable organic change and that hypertension is due to one or more disorders of function in the neuropsychic, endocrine and renal systems. The facts and interpretations on which these theories are founded may be summarized briefly as follows:

*Assistant in medicine, Massachusetts General Hospital.
†Physician, Massachusetts General Hospital.

The *kidney* is said, by the adherents of the renal theory, to be the essential organ in the cause of continued arterial hypertension for the following reasons: reduction in the amount of functioning kidney tissue, especially if the remaining tissue is injured, results in hypertension; alteration of the renal circulation to produce ischemia in animals is almost always followed by hypertension; a substance (or substances) is elaborated by the ischemic kidney that causes elevation of the blood pressure, accompanied by vasoconstriction; the endocrine nature of the kidney, apart from its excretory function, has been demonstrated,[5, 6] and humoral regulation of the blood pressure by the kidney in experimental hypertension, in shock, and possibly in normal states, is known to exist,[7-10] and, finally, the ischemic renal-pressor mechanism is independent of sympathetic or other innervation of the kidney, but requires the presence of the adrenal gland, if not as a primary, at least as a secondary participant.

The interpretation of essential hypertension as a general neurohumoral disease due to functional disorders with laboratory manifestations in the kidney may be stated best in terms of Selye's theory (the general adaptation syndrome). Challenge (psychic or physical stress, endocrine or electrolyte burdens, infection, congenital defect) leads to response (homeostasis of Cannon, the general adaptation syndrome of Selye), which is mediated by pituitary activity, which in turn stimulates adrenal activity. Adrenal activity causes renal vasoconstriction or renal ischemia. This leads to liberation of renin (acutely) accompanied or followed by one or more antienzymes or other pressor-depressor substances, which produce general vasoconstriction and organic change, especially in the small arteries.

It seems to us that the general theory of the adaptation syndrome as applied to the etiology of hypertension is a most useful hypothesis, since it brings some order to the mass of experimental work, including experimental renal hypertension, and since it offers a rationale by which the many recommended treatments may be judged.

According to the neurohumoral theory, the *pituitary gland* is the foremost of the mechanisms involved in hypertension. Stress may result in a catabolic process that causes elaboration of the pituitary corticotrophic hormone. This, in turn, increases adrenocortical activity, and so on. Removal of the pituitary gland prevents this stress hypertension and nephrosclerosis.[5] Renal experimental hypertension is not affected by hypophysectomy according to Goldblatt,[11] but is reduced to near normal accord-

ing to others.[12] Thus the pituitary is involved necessarily in one form of experimental hypertension, whereas in others it may or may not necessarily be involved.

In the Cushing syndrome, with its hypertension, arteriosclerosis, coronary-artery and renovascular disease, the pituitary gland may be involved (basophil adenoma almost always shows some microscopical changes in the basophil cells), and there may be hyperplasia or carcinoma of the adrenal cortex.[13] It has been suggested by Heinbecker that pituitary degeneration is caused by depression of the hypothalamic nuclei, and that the pituitary eosinophilic cells are thus stimulated. In turn, the adrenal cortex is stimulated, with the release of cortical hormones causing various effects. Among other things, this leads to constriction of efferent glomerular arterioles of the kidney, with the release of renin, which together with other reactions causes the hypertension. It is further suggested by Heinbecker that central-nervous-system influences, particularly from the frontal lobes, may depress the hypothalamic nuclei, initiating changes in the hypophysis and leading to the whole chain of events.[14-16]

Aspects of this hypothesis have been reviewed by Findley.[17] He believes that it assigns to the central nervous system the important role in the pathogenesis of hypertension and allied diseases that it deserves. Heretofore, the vasomotor centers have received consideration because of the great importance of the adrenergic system in the adjustment of the organism to emergency situations, but there is no convincing evidence that sympathetic tone is increased in chronic essential hypertension. One should seek to find anatomic evidence of hypothalamic disease and basophilic degeneration in all cases of continued diastolic hypertension, but Rassmussen was unable to do so. No structural changes need be anticipated, however, if one assumes that chronic hypopituitrinemia can be produced in constitutionally susceptible persons by sustained inhibition of the hypothalamus from impulses arising from the higher centers of the brain. This theory accounts for the fact that no chemical evidence of increased hormonal production is usually found.

The neurohumoral hypothesis may explain the fact that hypertension of purely renal origin eventually becomes nonrenal, the experimental observations being supported by clinical experience that nephrectomy seldom modifies the hypertension associated with unilateral renal disease unless the operation is done early.[18] Heinbecker considers that renin production increases whenever the integrity of renal tubular tissue is threatened by disease or anoxia, and that the resulting hypertension, produced by constriction of extrarenal blood vessels, is a compensatory phenomenon designed to maintain renal blood flow and glomerular filtration rate, and is sustained by the neurohumoral mechanism previously described. If so, this compensatory effort performs its task at great expense to extrarenal organs and eventually destroys the kidney itself by producing vascular lesions. It is much too early to attempt a correlation between these views and those offered by Shorr et al.[10] concerning the importance of vasoactive materials from the kidney and liver in the regulation of the circulation.

The *adrenal cortex* is the second important mechanism in the physical basis of continued arterial hypertension according to the theory of the general adaptation syndrome because disease that diminishes or ablates the adrenal cortex lowers the blood pressure in a patient with hypertension, and results in hypotension in the normal subject. Moreover, administration of the adrenocortical hormone restores the blood pressure to hypertensive or normal levels in such patients.[19] Pituitary corticotrophic hormone causes hypertrophy of the adrenal cortex, with production of adrenocortical hormones, and, when the animal is sensitized by high-protein or high-sodium diets, causes hypertension via the kidney with salt retention and diffuse vascular change.[5] Finally, certain tumors, or hypertrophy of the adrenal cortex as in Cushing's syndrome, are associated with hypertension; removal of the tumor, appropriate reduction of the hypertrophied adrenal cortex, or reduction of pituitary corticotrophic hormone is followed often by reduction of the blood pressure.

In the application of the theory of the general adaptation syndrome to the etiology of hypertension, the renal mechanism is considered to follow the adrenal cortex and to depend upon its being affected in one of two ways. Either vascular change in the kidney is induced, with resulting hypertension, or general hypertension is caused, which induces renovascular change. According to this view, the kidney is involved in the last stage of the mechanism, both functionally and organically. Thus, one should not say, according to the adaptation syndrome, that all hypertension is renal in origin but rather that all hypertension involves the kidneys, either functionally or organically.

General theories of etiology involving the renal, endocrine and nervous systems having been discussed, the recent important investigative work in each field is next reported.

The Renal System

The last fifteen years has constituted what one might call the "Goldblatt" era. Interest in the renal origin of hypertension was renewed when Goldblatt[20] reported his first work on the subject in 1934. The theory of the "renin system" was evolved in this country by Page and his co-workers and in South America by Braun-Menéndez and his colleagues. The work of the South Americans was

brought together in a monograph called *Renal Hypertension*, recently published in this country,[21] after having been brought up to date by Dexter. A later discussion by Dexter[8] presents the following possibilities: the "renin system" has nothing to do with the development and maintenance of experimental hypertension (this is suggested by the absence of renin in the blood of animals and patients with chronic hypertension[22, 23]); renin may initiate renal hypertension, and subsequently another pressor system (neurogenic) may take over[18]; and the amount of renin needed for maintaining chronic hypertension may be too small to be detected by present methods. The failure to find sufficient renin in the blood of patients and animals with chronic hypertension has been reported by others.[24, 25] The latter of these papers describes the use of a method satisfactory for the enzymatic determination of small amounts of renin. Of 21 patients studied, 17 tests were negative, 1 moderately positive, and 3 slightly positive. The quantity of renin indicated in the 3 positive results was too small to account for even a minimal pressor effect on intravenous injection.

One of the outstanding contributors to the understanding of renal physiology, Homer Smith,[26, 27] is of the opinion that renal ischemia is the result and not the cause of hypertension. In his studies of effective renal blood flow in 60 cases of essential hypertension, renal ischemia was found in many of the patients. It was possible to reverse the ischemia when hyperemia was induced. Renal ischemia was interpreted, therefore, as one of the sequelae of the disease, and not as the cause of it. The fact that reduced renal blood flow is present more frequently in hypertensive patients than in those with normal blood pressure has been confirmed by others.[28, 29] Hilden[28] expressed the opinion that essential hypertension is probably due to renal ischemia, whereas Bolomey and his associates[29] did not commit themselves but were satisfied with the statement that decreased renal flow is known to accompany hypertension. An interesting experiment on renal blood flow was reported by Forster et al.[30] Experimental hypertension was produced in animals by cutting of the moderator nerves, after which clearance technics were used to measure the effect of pressure increase on the renal blood flow and glomerular filtration rate. A mean blood-pressure rise of 43 per cent was accompanied by an increase in renal blood flow of 5 per cent and an increase in glomerular filtration rate of 8 per cent. Had the animals been watched and rechecked for effective renal blood flow at intervals, this information might have contributed to the answer of the much-debated question of whether the kidney is the victim or the culprit in hypertension. For if the effective renal flow tends to become diminished after a period of hypertension produced by cutting of the moderator nerves, this would be evidence in favor of the victim theory.

Hughes-Jones and his co-workers[31] introduce their discussion by referring to work done by Pickering and Prinzmetal in 1940 showing that after the intravenous injection of renin, the urine flow was at first reduced but subsequently rose to high levels. Inasmuch as the vascular effects of renin are presumably due to the formation of hypertensin, these workers were curious about the effect of hypertensin itself on renal function. The unanesthetized rabbit was used, and hypertensin was given intravenously. The result was an increase in the rate of urine flow and an increase in chloride excretion. The chief action of hypertensin was thought to be in the tubules distal to the proximal convolutions, and the effect was thought to be mediated by the vascular system. The authors suggested that the blood might be diverted from the glomeruli supplying the short loops to those supplying the long loops, which plunge deeply into the medulla; thus they evoked the work of Trueta.[32] Their results were consistent with the hypothesis that the action of renin on the kidney, as well as on the blood vessels, is mediated by hypertensin.

The renin-hypertensinogen-hypertensin mechanism was considered critically by Mylon, Lund and Heller,[33] whose conclusions were at variance with those of the English workers just discussed, but it should be noted that the experimental animal of Mylon et al. was the dog rather than the rabbit. Their study indicated that blood pressure responses to renin could not be explained by the production of hypertensin. Renin and hypertensinogen were incubated in such a way that the resultant product should have been hypertensin. The intravenous injection of the material gave an increase of blood pressure to limits that did not exceed 100, whereas the intravenous injection of renin gave a rise up to 160 to 180. This work suggests that renin is a more powerful pressor substance than the material postulated in the "renin system" as being the really effective material.

A pressor agent, presumably derived from the kidneys, but different from hypertensin, has been described by Shipley, Helmer and Kohlstaedt.[34, 35] Cats subjected to a period of hypotension by bleeding were shown to have a pressor principle in the blood plasma. This was obtained from cats with intact kidneys, but not from cats whose kidneys had been removed previous to the period of hypotension, nor in the blood of normal living cats, nor in cats that had been killed suddenly. These findings suggested that the pressor agent arose from the kidneys, being formed as a result of low blood pressure. In further work,[36] these authors found that when the pressor agent was injected in cats nephrectomized only a few hours previously, elevation of blood pressure was much less than that in cats nephrectomized two days prior to injection. Three

possible explanations were considered: the kidneys may secrete a substance that is an inhibitor, or otherwise functions as an antagonist, to the sustained pressor principle; the hypothetical inhibitor spontaneously disappears from the animal after bilateral nephrectomy; and the inhibitor substance is neutralized or rendered ineffective by repeated intravenous injections of the plasma containing the pressor principle.

Grollman[37, 38] has attempted in recent years to prove two main points: that hypertension is caused by the reduction in the number of functioning nephrons and is not due merely to renal ischemia or intrarenal vascular change; and that the normal kidney exerts a benign influence on the blood pressure. The question of species difference always comes up when the experimental work of Grollman is discussed, for he has generally used the rat. Other workers contend that the rat is a hypertensive-susceptible animal, and that results obtained from experimental work with the rat are therefore difficult to evaluate. A figure-of-eight ligation of one or both kidneys has been used routinely. The resulting hypertension was interpreted as being due to the reduction in the number of functioning nephrons. Since the interpretation was questioned, experiments were performed that were designed to prove their point. Hypertensive effects were produced simply by removal of one kidney, thus reducing the number of functioning nephrons.[39] Again, the results of this work were questioned, for other workers had not obtained the same results after unilateral nephrectomy, and indeed, in the human being there is little clinical evidence to support this point of view.[27, 40] Grollman's contention has been that the development of hypertension depends on the presence of lesions in the remaining kidney. Ogden[18] has summed up the difference of opinion in his suggestion that the removal of the ischemic kidney during the first month usually abolishes hypertension, whereas the hypertension persists if the kidney is removed after three months.

Grollman has pointed out that the exact role of the kidney in the pathogenesis of hypertension has been difficult to determine because of the impossibility of ablating the organ without introducing fatal effects. In an effort to demonstrate the effects of ablation without the usual fatal effects, the experimental animals were maintained in fair condition on an electrolyte-free diet and by the use of Kolf's artificial kidney.[41] Bilateral nephrectomy resulted in hypertension in 28 of 38 dogs.[42] The usual pathologic tissue changes associated with malignant hypertension were observed.[43, 44] It was argued that in this case hypertension could not be due to the liberation of renin or other pressor agents derived from the kidney, but probably resulted from the failure of the functions ordinarily performed by normal kidney tissue.[45]

Hartroft and Best[46] produced severe renal damage and subsequent hypertension in rats on a diet deficient in choline. The lesions were primarily tubular, the glomeruli being secondarily involved. After an appreciable number of glomeruli were destroyed, a train of events was started that eventually led to hypertension. The effect of the protein content of the diet on rats has been reported,[47] and the plasma protein concentration found to vary with the amount of protein in the diet. In human beings one cannot so readily bring about a change in plasma concentration no matter whether the protein is taken by mouth or given parenterally. Considerable work has been done by Addis and his associates[48] on the effect of renin in rats; similar work was done with rabbits by Pickering and Prinzmetal in 1940. They found, as earlier investigators did, that renin induced hypertension and a proteinuria. It is of interest that adrenalectomy abolished the proteinuric effect of renin. The tachyphylaxis often observed in the past was reported, and it was suggested that the inactivity of renin with respect to its pressor effect led to a loss of its capacity to induce proteinuria.

The renin problem has been investigated over a period of years by Wakerlin and his colleagues.[49, 50] Much of their work has been summarized recently. The renin concentration of 500 dog kidneys was determined and found to be relatively constant. Renin disappeared from the contralateral kidney twenty days after unilateral renal-artery constriction. Unilateral nephrectomy had no effect on the renin concentration or on the level of the blood pressure. The authors believed that the results of these experiments argued neither for nor against the renin-hypertensin hypothesis of the pathogenesis of renal hypertension; to us, these results appear to be potent arguments against the renin-hypertensin hypothesis. These authors have also been interested in the treatment and prophylaxis of experimental renal hypertension. Because of their normal pulmonary pressure, lung extract was injected into hypertensive dogs in the hope of inducing a hypotensive effect, but without success.[51]

The effectiveness of hog renal extracts in the treatment and prophylaxis of experimental hypertension in the dog has been the subject of many reports. Various crude extracts have varied in effectiveness, and this difference has been found to be due to the fact that the early extracts were prepared from the whole hog kidney. Recently, dogs treated prophylactically with renin prepared from the cortex were protected against experimental renal hypertension, whereas none of the dogs treated with extract prepared from the whole kidney were protected. Similarly, the cortical extract was more effective against experimental malignant hypertension than the whole kidney extract. Purified hog renin was found to be effective in the treatment of renal hypertension in dogs. The results suggested

to the authors the antirenin theory as the mechanism of these therapeutic and prophylactic effects.[52]

In 1947 Trueta and his co-workers[32] described studies on renal circulation. An experimental method for producing ischemia of the renal cortex in rabbits was described. After the application of a tourniquet to the limb of the rabbit, they observed a constriction of renal arteries and dilatation of the veins with a more rapid appearance of the contrast medium in the renal vein than occurred without this manipulation. Similar vascular changes could be produced by stimulation of the sciatic nerve or the distal end of the splanchnic nerve, an observation suggesting that a nervous reflex mechanism was responsible for the vascular effects of the tourniquet. A short-circuiting of the blood in the rabbit kidney, occurring through the vasa recta of the medulla and resulting in an ischemic condition of the cortex of the kidney, was inferred. They postulated that this pathway serves only passively as a by-pass in normal kidneys, but causes a permanent diversion in the abnormal kidney; the "shunt" operates normally during emotional disturbances, but excessive operation of this normal mechanism may cause anoxia of the renal cortex similar to the results produced by sclerosis of the vessels of the kidney. It was suggested that this is a method by which renal ischemia can be caused in the human being, with resulting hypertension.

Clearance tests should be interpreted with caution. The work of Selkurt[53, 54] is cited as a confirmation of this opinion. Selkurt reported discrepancies between the renal blood flow as calculated by clearance tests and that determined by direct measurement. Observations were made after the release of the clamp that had occluded the renal artery for a period of twenty minutes. A marked disparity between actual renal blood flow and that calculated by clearance tests was noted. This study seems important since the conclusions drawn from clearance tests are only inferential. Trueta's interpretation of this discrepancy was that it was a result of blood diverted from the cortex to the medullary pathways.

The work of Trueta has led to other investigations. Black and Saunders,[55] by stimulating the sciatic nerve in rabbits, attempted to determine the effect of the shunt on renal function, as assessed by inulin and p-aminohippuric acid (PAH) clearance. The general pattern was a lowering of the inulin and PAH clearances together with a rise in the ratio of inulin to PAH clearances. The authors found it difficult to relate these changes to the shunt, for a constriction of the efferent arterioles may produce the same clearance changes. In another report, painful stimuli were said to cause antidiuresis due to a decrease in the renal blood flow and filtration rates.[56] Conceivably, this could be explained by diversion of the renal blood through the medullary by-pass, as described by Trueta, but the glomeruli excluded from the circulation were uniformly dispersed in areas receiving good circulation through adjacent glomeruli. Reubi and Schroeder[57] attempted to determine whether a renal shunt could be produced in human beings and in dogs by vasoactive drugs. Their results did not support Trueta's hypothesis of the intermittent operation of large shunts responsible for ischemia of the renal cortex. Other workers carried out observations on the circulation and renal function in human subjects with normal renal function.[58] The subjects were given epinephrine parenterally, which resulted in a reduced renal plasma flow, accompanied by a rise in filtration fraction. This was thought to imply a constriction of the efferent arterioles. A similar effect could be expected as a result of emotional disturbances.

The characteristic microscopic *pathology* of continued arterial hypertension is not in itself pathognomonic, but its localization and intensity in the kidneys are characteristic of 97 per cent of patients whose deaths are due to this condition.[59] These changes are intimal proliferation, medial hypertrophy and intimal hyalinization of small arteries. One of the most important results of the surgical treatment of hypertension has been the opportunity to observe the adrenal glands and to perform biopsies on the kidneys of patients with hypertension in various stages of the disease. To date, gross observation of the adrenal glands has revealed tumors otherwise unsuspected, and with increasing knowledge of the role of the glands close inspection may supply further significant data. The most important recent contribution to the pathology of hypertension has been the data from renal biopsy in 500 patients with hypertension treated by sympathectomy reported by Castleman and Smithwick.[60] They believe that their material represents adequate sampling of the kidneys since their series of 500 cases agrees with the series of 100 first reported, since biopsies from both kidneys revealed the same grade of vascular disease in 75 per cent, and since there was a good correlation between biopsy grades and renal function by a qualitative test. There was a good correlation between biopsy grades and retinal-vessel changes applied to the lowest and highest grades, and finally of 61 patients under thirty years of age, 62.5 per cent had minimal or no renovascular disease. On a grading of 0, or no disease, to IV (severe arteriolar disease) 23.4 per cent of the biopsies were Grade 0 or I, and 22.5 per cent Grade II. Thus 45.6 per cent of the 500 cases had minimal or no vascular narrowing. The authors conclude that hypertension frequently exists in man without evidence of renovascular disease or with insufficient evidence to explain the elevated blood pressure.

There have been some differences of opinion regarding the etiology of malignant nephrosclerosis. In the Goldblatt[11] experiments the arterioles beyond

the clamps did not show the arterial necrosis characteristic of malignant renovascular disease, whereas such changes may appear in the arterioles elsewhere. He concluded that not only greatly increased vascular tension but also renal insufficiency is necessary for the development of malignant nephrosclerosis. Wilson and Pickering[61] confirmed this observation in rabbits, concluding that greatly increased intra-arterial pressure is the chief factor. Recently, Byrom and Dodson[62] confirmed these observations in rats and demonstrated that brief artificial distention of the arterial tree caused typical focal arterial necrosis, the smaller arteries of the kidney being selectively vulnerable. They believe that neither actual renal failure nor absorption from injured renal tissue are necessary to produce arterial necrosis. Admittedly, it is somewhat hazardous to conclude too much from the experiments on rats since this animal is so susceptible to spontaneous renal infection and to hypertension. Nevertheless, it is suggested that increase in blood pressure precedes the renal changes even in malignant hypertension, as the biopsy studies of Castleman and Smithwick seem to show in the benign form of continued hypertension.

Endocrine System

Although the amount of work that has been done on the renal origin of hypertension has been of extraordinary proportions and has been rewarding in many respects, we believe that the question of the etiology of hypertension remains unsolved. One objection to the renin-hypertensin theory, which no one has been able to answer and which most investigators have assiduously avoided, is the production of tachyphylaxis by renin. Furthermore, if change in the renal dynamics is necessary to start the train of events, what is the change in the vascular system of man that occurs with sufficient frequency that one might accept it as a starting point? If hypertension itself is the condition that brings about the change in renal dynamics, one can no longer accept the thesis that the kidney is the culprit. Stress, and its effect upon susceptible persons, or perhaps we should say on persons with susceptible cardiovascular systems, seems a more acceptable starting point in the train of events that finally leads to essential hypertension. Walter Cannon first brought the idea of stress prominently before the minds of investigators. Although his own work led him more along the neurohumoral system, it was his thought that resulted in the realization that stress causes tremendous changes within the body.

The adrenal gland has been the subject of interest and speculation for at least half a century. First, the medulla with its secretion of a pressor substance, and later the cortex became the object of attention. Desoxycorticosterone acetate (DCA) was the first of the adrenocortical steroids to be produced synthetically. The use of this material in Addison's disease, with the elevation of blood pressure as one of the results, led to its use in the study of hypertension. There have been several studies reported recently in which DCA has been used with and without sodium chloride. Knowlton and others[63] used DCA and sodium chloride in both nephritic and nonnephritic animals. It was found that arterial hypertension developed in the former but not in the latter. In the normal rats DCA and sodium chloride caused only enlargement of the heart and kidneys but no increase in blood pressure. This work suggested that DCA produces hypertension only when the kidneys are abnormal. The same effect of the development of hypertension in in the human being when the kidneys are damaged is suggested by the paper by Altschule and Zamcheck.[64] Another group of workers attempted to show that the kidneys were not involved.[65] Two groups of animals were used, one being given DCA and sodium chloride and the other only sodium chloride. After total nephrectomy, the treated animals (DCA pellets) continued to show a rise in blood pressure, whereas the blood pressure of the control group remained unaltered. Working on much the same problem the Friedmans[66] made a similar observation: after the removal of both kidneys in DCA-treated rats, the blood pressure continued to rise. Their interpretation differed from the foregoing one; it was their opinion that the kidney is actively concerned with the excretion and the possible inactivation of the steroid. Observations by Selye and Stone[67] indicated that lesions in the kidneys and heart could be produced by continuous exposure to various kinds of stress or by treatment with anterior pituitary corticotrophic preparation as well as DCA, but that these agents were effective only when the diet included considerable amounts of sodium chloride. Friedman and his co-workers[68] undertook a study to determine whether the adrenal gland liberated a factor that opposes the action of DCA. This study was apparently inspired by observations of Pines et al.[69] The results of Friedman and his co-workers confirmed the hypertensive effects of DCA and indicated that additional sodium chloride was not essential for the production of hypertension. Adrenocortical extract did not modify the hypertensive effects of DCA, and they concluded there is no antihypertensive factor in the adrenal glands.

It seems from the studies reported that DCA invariably causes an elevation of blood pressure in various animals whereas this is not by any means consistently true in the human being. Perera and his group have written extensively on the effects of DCA in human subjects. Their interest started when it was reported that DCA resulted in a rise in blood pressure in Addison's disease.[70] In using DCA in the treatment of Addison's disease, they observed that after many months of treatment, hypertension developed in 8 out of 24 patients.[71]

The hypertension was not ascribed to the restoration of the salt and fluid level, which occurred immediately, whereas the hypertension developed only after several months. Observations were later made on 16 normotensive and 14 hypertensive patients.[72] In both groups, there was an increase in weight, hemodilution, reduction in urinary volume and retention of sodium and chloride. No consistent alteration could be shown in the serum sodium and chloride, although there was a reduction in serum potassium. In the hypertensive patients, there was an increase in both systolic and diastolic pressures, whereas no change occurred in the resting blood pressure of the normotensive patients except after prolonged administration of DCA. This seemed to confirm Perera's original postulate that hypertension could not be ascribed to the retention of salt and water. At another time, the effect of DCA on 5 hypertensive patients was reported as giving rise to only small increases in resting blood pressure.[73] In this study the blood pressure of two of the patients returned to control levels while they were still on DCA; in the other 3, the blood pressure returned to control levels after the drug was discontinued. Adrenocortical extract, in contrast to DCA, caused an actual decrease in resting blood pressure in 3 of 4 hypertensive patients.[69] When DCA and adrenocortical extract were given together, minimal increase or actual decline in blood pressure was noted.[74] Goldman and Schroeder[75] used DCA on a group of patients. Four of these had coarctation of the aorta, and 3 had essential hypertension; the former showed little response, whereas the latter appeared sensitive to the material, responding with prolonged increases in the blood pressure and exacerbation of symptoms. The status of the kidney was not indicated, but if the results obtained by Knowlton in animals can be applied to human beings, one might conjecture that the patients with essential hypertension had damaged kidneys whereas the kidneys of the patients with coarctation were undamaged. This is further suggested by the fact that DCA did not cause a significant elevation of diastolic blood pressure in normal patients to whom it was administered. Thus, it appears from the evidence at hand that DCA acts to a certain extent on the peripheral vascular system, but that effects induced by it are normally balanced by other fractions of the adrenal cortex.

In the abnormal or unbalanced production of cortical steroids, several conditions are undoubtedly manifested, which may conceivably depend on the type of imbalance present. The two well known conditions, Cushing's and Addison's syndromes are examples of the extremes of abnormal endocrine status with respect to the imbalance of adrenocortical steroids. In some cases in human beings the administration of ACTH is said to be accompanied by an elevation in blood pressure, whereas in others an insignificant rise has been reported. Several workers have shown that stress is associated with an increase in adrenocorticotrophic hormone (ACTH). Selye, in his monograph, theorizing about the mechanism of observed changes, suggested that an organism subjected to stress liberates toxic metabolites that stimulate the anterior lobe of the pituitary gland to discharge adrenotrophic hormones, these in turn stimulating the adrenal cortex to produce an excess of cortical hormones and thus increasing the resistance of the body. The diseases of adaptation, of which hypertension is one, are considered to be the result of this defensive endocrine response, for the overdosage of endogenous hormones then becomes the cause of certain cardiovascular, renal and joint diseases.

In 1947 Long[76] reviewed the work that he and his group had done over a number of years. When ACTH was injected into a rat, there was a decrease in the cholesterol and ascorbic acid content of the adrenal gland. A similar result was observed in animals that were subjected to stress, and in this case it was inferred that there was a release of ACTH from the anterior lobe of the pituitary gland. The decrease of cholesterol and ascorbic acid observed in the adrenal glands as a result of ACTH was accompanied by definite physiologic indications of an increased output of cortical hormones. In the hypophysectomized animal, no change in the adrenal constituents was observed; thus, it seemed that the pituitary gland was necessary for activation of the adrenal cortex. Long, speculating about the mechanism of activation of the adrenotrophic hormone secretion, suggested two possibilities: changes in composition of blood traversing the gland; and nervous control. In discussing the latter, he pointed out that all types of stress are accompanied by the same type of nervous activity — the excitation of the autonomic nervous system with release of epinephrine. To test out this idea, epinephrine was injected, and a decrease in adrenal cholesterol and ascorbic acid was again noted. Epinephrine was ineffective after hypophysectomy. The question was raised whether epinephrine is just another form of stress or the common mechanism by which all forms of stress are carried to the pituitary gland.

Sayers and Sayers,[77] working on the same general problem of the means of activation of the pituitary gland and the subsequent release of the hormone, administered ACTH to rats immediately before exposure to stress and found that the adrenocortical activity provoked by stress was suppressed. This was interpreted to mean that the anterior pituitary gland elaborated ACTH at a rate inversely proportional to the concentration of cortical hormones in the body and according to the requirements of the peripheral tissues for cortical steroids. These workers also attempted to distinguish the quantitative potency of five crystalline steroids to inhibit the activity of the pituitary gland. This was done by injecting the various

materials and then subjecting the animals to some form of stress. The cholesterol and ascorbic acid content of the adrenal glands was the end point used in the determination. The 17-hydroxy-corticosterone and corticosterone, two of the steroids primarily concerned with intermediary protein and sugar metabolism, were assigned as the most potent pituitary inhibitors. These conclusions offer support to the following work.

Deane and Greep[78, 79] have presented some interesting observations of the adrenal cortex of the rat. Their results at first seem hard to reconcile with those of the other investigators as well as with accepted clinical effects. After removal of the pituitary gland, the adrenal cortex atrophied rapidly in the rat. This atrophy, however, was the result of shrinkage of the fasciculata or inner zone of the cortex, whereas the glomerulosa or outer zone showed a compensatory hypertrophy. In the adrenal cortex of the rat, the inner zone or fasciculata has been shown to produce the steroids effecting sugar and protein metabolism, and the glomerulosa produces the salt and water hormones (Swann[80]). Administration of ACTH prevented the atrophy of the fasciculata in the hypophysectomized rat. The conclusion reached by these authors was that in the rat the outer zone of the adrenal cortex was not under the control of the pituitary gland, whereas the fasciculata, the zone producing sugar and protein hormone, was subject to pituitary control.

Although results obtained by Deane and Greep have been thought to be due to a species difference, it is interesting that the rat is the animal generally in use for the work on the adrenal cortex, and much of what is now accepted has been inferred from experimental work on the rat. Ingle, Li and Evans[81] used ACTH on rats and noted certain metabolic changes that indicated that this hormone stimulated the secretion of the adrenal steroids that affect organic metabolism. Sodium retention was not observed. They noted that the hypophysectomized animal does not lose vital amounts of sodium and chloride as the adrenalectomized animal does, and suggested that the secretion of active sodium-retaining steroids by the adrenal cortex may be independent of ACTH. Ingle and his group[82] also compared the metabolic responses of normal rats to ACTH as related to diet, which in their studies involved forced feedings of high-carbohydrates, high-fat and high-protein diets. On the high-carbohydrate diet, some of the rats developed glycosuria. An inhibition of weight gain and an increase in urinary nitrogen and potassium were observed in all the animals, but were most marked in those given high-fat diets and least in those given high-protein diets. Small, temporary increases in the excretion of sodium and chloride occurred. In none of their experiments, did they observe sodium and chloride retention.

Bergner and Deane[83] later commented on the difference in the effect of ACTH on rats and man, and noted that in the rat, salt retention did not follow the administration of the hormone, which in man had been found to cause marked salt retention; they cited the work of Forsham et al.[84] The preparation of ACTH used by Forsham and his co-workers was not a homogenous protein as was Li's material, employed by Mason and his associates,[85] who observed no sodium and chloride retention in their studies on a normal woman. Although the properties of one steroid compound, 11-desoxycorticosterone, relating to the electrolyte balance are well known, relatively little is known of the other biologically active adrenocortical steroids, according to Ingle et al.[82] The whole subject is very complex, as indicated by the fact that although 28 steroid hormones have been isolated from cortical extracts, the amorphous fraction that remains has factors capable of maintaining life in adrenalectomized animals. It may be that as more is known about this amorphous fraction, and as the properties of the already isolated steroid hormones are elucidated, some of the gaps in the understanding of the etiology of hypertension will be filled.

(To be concluded)

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

BENJAMIN CASTLEMAN, M.D., *Associate Editor*

VIRGINIA W. TOWNE, *Assistant Editor*

CASE 36331

PRESENTATION OF CASE

A sixty-six-year-old man was admitted to the hospital because of increasing shortness of breath.

The patient was well until twenty months prior to entry, when he was suddenly seized with a severe, squeezing pain in the precordium. Medication given by his physician relieved the pain. An electrocardiogram confirmed the diagnosis of coronary thrombosis. After two months of bed rest the patient began to be ambulatory, but because of increasing dyspnea on exertion he had led a bed-and-chair existence for the past eight months. During this time he developed increasing dyspnea and orthopnea at night. He had an occasional constricting sensation in the neck but no frank chest pain and occasional lower mid-abdominal discomfort lasting ten to thirty seconds and relieved by hot-water bottles. After the attack twenty months before entry he was given digitalis, 0.1 gm., every day, and at the onset of dyspnea the dose was increased to 0.2 to 0.3 gm. every day. For the past five months he was given an intravenous injection every week to increase the urinary output. He had no ankle edema. He had been on a regular diet without added salt. His symptoms had increased and had not responded to treatment during the last two months.

Physical examination revealed a dyspneic, elderly man sitting up in bed. The neck veins were elevated and pulsating. The chest was increased in the anteroposterior diameter, with limited expansion. The lungs were clear except for a very few inspiratory rales in the lower lateral chest bilaterally. There was slight dullness at the right base. The heart was enlarged, with the point of maximum impulse at the anterior axillary line in the fifth left interspace. There was no gallop, rub or murmur. The abdomen was soft, with no masses or tenderness. The spleen and liver were not made out. Rectal examination was negative. There was no ankle edema. Neurologic examination was negative.

The pulse was regular at 100, and the respirations 22. The blood pressure was 100 systolic, 80 diastolic.

The urine gave a ++ test for albumin and a + test for sugar; the specific gravity ranged from 1.020 to 1.012; the sediment contained many hyaline and rare granular casts. The white-cell count ranged from 5800 to 8300, with 68 per cent neutrophils. The stools were guaiac negative. The nonprotein nitrogen ranged from 38 mg. on admission to 190 mg. per 100 cc., and the chloride from 86 to 95 milliequiv., the sodium from 123 to 129 milliequiv., the potassium from 5.5 to 6.5 milliequiv., and the carbon dioxide from 22 to 26 milliequiv. per liter. X-ray examination revealed a markedly enlarged heart and pulmonary findings consistent with congestion and edema with pleural effusion. An electrocardiogram disclosed sinus tachycardia (rate of 130). The P-R interval was 0.17 second and the QRS complex equaled 0.08 second. The axis was normal. The Q waves were small in Leads 1 and AVL. The S waves in Lead 3 were slurred. The T waves were flat in Leads 1, AVL, F, V_5 and V_6, low and upright in Leads 2 and 3, and upright in Leads V_1 through V_4.

The patient was given, in addition to digitalis, 0.1 gm. every day, digitoxin, 0.2 mg. and 0.3 mg., ten and eighteen hours after admission, respectively, 2 cc. of Mercuhydrin and enteric-coated ammonium chloride, 1.0 gm. three times a day. On the following morning he was nauseated and began to vomit. He had diuresis of some four and a half pounds. On the following day he complained of lower abdominal discomfort and was very apprehensive. Examination showed many ventricular premature beats. He continued to be nauseated and to vomit for the next four days and also to have severe sharp abdominal pain coming on in spasms and lasting thirty to forty-five minutes. During this period the fluid intake was poor, averaging 1500 cc. On the fifth hospital day the nonprotein nitrogen was 94 mg. per 100 cc. The oral intake was increased to 2000 to 3000 cc. On the eighth day the nonprotein nitrogen was 150 mg. per 100 cc. and the chloride 82 milliequiv., the sodium 123 milliequiv., the carbon dioxide 22 milliequiv. and the potassium 6.5 milliequiv. per liter. The output averaged approximately a third of the intake. During the subsequent days efforts to increase the fluid intake by 10 per cent dextrose in water intravenously and forced fluids were unsuccessful. Concomitant with four days of intravenous fluid supplement he developed ankle and sacral edema. On the eighth hospital day he became disoriented and confused, had Cheyne–Stokes respirations intermittently and presented persistent signs of congestive failure—distended neck veins, peripheral edema, sacral

edema, slight hepatomegaly, poor heart sounds and a blood pressure ranging from 70 to 90 systolic, 60 to 70 diastolic, a pulse rate of 100 to 110 and scattered moist basal rales. On the tenth day he developed watery diarrhea lasting for four days. On the twenty-first day the nonprotein nitrogen reached 190 mg. per 100 cc., and the chloride 85 to 90 milliequiv. per liter. The physical status had changed little. Because of the low blood pressure it was difficult to find veins for intravenous feeding. He had intermittent complaints of lower mid-abdominal discomfort.

On the thirty-sixth day the patient became stuporous, the temperature rose to 102°F., respiration became labored, and he died.

Differential Diagnosis

Dr. Alfred E. Kranes*: Do you know, Dr. Mallory, whether or not the urinary output was increased by the intravenous injections?

Dr. Tracy B. Mallory: I do not believe we know anything more than the statement recorded.

Dr. Kranes: I presume that the Mercuhydrin was given when the patient was first admitted to the hospital.

I shall start by assuming the correctness of the original diagnosis of myocardial infarction, for there seems little reason to doubt it. The evidence presented here is quite consistent with such a diagnosis. It might be of some interest to see the x-ray films even though they do not contribute much to the final problem.

Dr. Stanley M. Wyman: I think there is very little to add to the record. The rather large quantity of fluid in the right pleural space is well seen, and there is a smaller quantity in the left. The heart shadow is considerably enlarged, particularly in the region of the left ventricle. A tortuous aorta is noted. There is considerable pulmonary congestion and some superimposed central edema. This film of the abdomen, taken a week after the chest films, shows no apparent gross abnormality of the viscera. The kidneys are fairly normal in size and shape. The liver may be a little large. There is nothing to suggest intestinal obstruction or stones.

Dr. Kranes: We have, as the problem for discussion, the reason for this patient's uremia. In that connection two questions are raised: Was this uremia due to intrinsic disease of the kidney, and, if so, what was the nature of the kidney disease? To answer the first question, one must first consider the various extrarenal mechanisms that might produce the picture described here. In reading this protocol one is immediately struck by the resemblance of this picture to that seen in acute adrenal failure. This patient had a low blood pressure, various gastrointestinal symptoms, marked loss of sodium and chloride, weakness, and finally some fever, so that one has a right to ask whether this could possibly have been adrenal failure. Although it bears considerable resemblance to that syndrome, it seems unlikely that a patient with adrenal failure, to whom no substitution therapy was given, could have lived thirty-six days. Although I think it possible that adrenocortical failure played some role in the ultimate production of this picture, I do not believe any anatomical evidence of adrenal failure is likely to be found.

In view of the lower abdominal pain that recurred throughout this history, one wonders whether a malignant lesion could possibly have been present somewhere, producing peritoneal implants and ureteral obstruction, since the urinary output had been so meager. If such a lesion was present, I do not see how it is possible for us to make the diagnosis. Apparently, the physicians who were taking care of this patient were not unduly concerned about the abdominal pain since no studies of the gastrointestinal tract were made. It therefore seems that some intrinsic disease of the kidney or some profound disturbance of renal physiology must have been going on here. What the nature of the renal lesion was I am sure I do not know. Some time ago, I asked Dr. Castleman not to present me with any more patients dying in uremia. Trying to predict the renal lesion in these cases is likely to be a most unrewarding exercise. But he keeps on trying me, and perhaps some day I shall succeed in arriving at a correct solution to one of these problems.

This might have been almost any type of renal disease. It could have been an acute glomerulonephritis although there was not much clinical evidence for such a process. The disease does occur in elderly people. We have seen it even in the absence of hematuria. I see no way of ruling it out although it seems unlikely. Other types of kidney disease such as pyelonephritis also seem unlikely but possible. Even though there was no obvious cause for it, lower-nephron nephrosis is a possible mechanism for the patient's renal failure. I do not see how we can rule in or out any of these considerations, or any other type of renal disease, for that matter.

We have a right to ask what role this patient's therapy played in the production of the illness. One must remember that he was on a regime of treatment that resulted in severe salt deprivation. The salt intake was restricted; he was put on ammonium chloride, which leads to a loss of sodium — whether any ammonium chloride was given prior to admission is not stated; finally, and most important of all, he was given repeated doses of Mercuhydrin. The first question raised is what role Mercuhydrin played in the production of this picture. There are few authentic cases of direct renal injury from the administration of Mercuhydrin, although occasional questionable ones have been reported. One would think that if this were a

*Associate physician, Massachusetts General Hospital.

factor renal injury would be encountered more often, considering the extreme frequency of mercurial administration. Mercuhydrin may damage renal physiology not by any direct action of the mercury but because of its propensity for causing sodium loss. We have in operation here, therefore, three factors leading to a loss of salt as indicated by the blood chemical findings. Ever since the introduction and the widespread use of low-salt regimes in congestive heart failure, there are being reported, and all of us are encountering, cases in which this salt deprivation has led to renal failure. Just how it does so I am sure I do not know.

I was discussing this problem with Dr. Lewis Kane at lunch yesterday and he called to my attention a most informative paper by Schroeder* on the low-salt syndrome. Those interested in this problem will find this paper extremely profitable reading. Just how salt loss produces renal failure and uremia is not known although various mechanisms have been postulated. It is very likely that salt loss leads to diminished renal blood flow, a diminished glomerular filtration rate, oliguria and uremia. But other mechanisms may be involved, and a great deal more work needs to be done on this particular problem before it is properly elucidated. This probably only occurs in patients who have kidneys that are already slightly damaged, although there are occasional cases in young persons in which severe salt loss has led to renal insufficiency even in the presence of presumably normal kidneys with some degree of pre-existing renal insufficiency; severe salt loss accentuates the whole problem in some obscure way.

If this explanation is correct, I think we can understand why the attempted therapy in this patient led only to a worsening of his state. The administration of large amounts of water — particularly glucose in water intravenously or water low in salt content taken by mouth — will tend only to make the situation worse. The record shows that concomitant with four days of intravenous fluid supplements, he developed ankle and sacral edema, and on the eighth hospital day he became disoriented and confused, and had Cheyne-Stokes respirations and a rising nonprotein nitrogen. That is just what one might expect to occur in a patient with a very low extracellular salt if much water is given. It simply dilutes the extracellular salt and diminishes it still further if the kidneys are unable to excrete the administered water. What these patients need is hypertonic sodium chloride in fairly large doses. We have become so accustomed to withholding salt from people with congestive heart failure that it does not seem proper to administer concentrated salt solution to a patient in this state. But it may be life saving. It may completely reverse the process, and it may actually diminish the congestive heart failure by the promotion of a diuresis.

I would guess that this patient had a healed myocardial infarction with congestive heart failure and that the kidneys probably would not show very much of anything anatomically. There may be some nephrosclerosis, perhaps some congestion, possibly even a glomerulonephritis or a pyelonephritis, but I believe that whatever is found anatomically probably would not explain this patient's death. I think it is improbable that the morphologic changes in the kidney would be severe enough to have produced death from renal failure and that some additional mechanism such as salt loss would have to be postulated.

I should also have pointed out that severe abdominal cramps are a frequent accompaniment of this syndrome, and that may have been the reason for them in this patient.

Clinical Diagnoses

Myocardial infarct, old.
Nephrosclerosis.
Uremia.

Dr. Kranes's Diagnoses

Low-salt syndrome, with uremia.
Myocardial infarct, old, with congestive heart failure.
Nephrosclerosis, slight.

Anatomical Diagnoses

(*Uremia due to low-salt syndrome.*)
Myocardial infarction, old.
Mural thrombi, left ventricle and right auricle.
Nephrosclerosis, slight.
Pulmonary infarcts, multiple.
Pseudoacinar degeneration of adrenal cortex.

Pathological Discussion

Dr. Mallory: About two weeks ago, when I was in Madison, Wisconsin, I was asked about renal failure due to sodium insufficiency and said I had not yet seen any example of it. I think that is probably what we are dealing with in this case today although I do not know how to make an anatomical diagnosis of such a condition. Dr. Kranes was entirely correct in predicting that there was no significant renal lesion despite the very high nonprotein nitrogen. The kidneys of any elderly man are never entirely normal, and we found some focal scars, probably on an arteriosclerotic basis, but in view of his age, I think it is fair to say that the kidneys were essentially normal. The adrenals were of a little interest although, again, it is difficult to interpret the findings. There was in the cortex of both adrenal glands a total depletion of lipids, which is a very nonspecific lesion, but there was also a rather marked degree of pseudoacinar degeneration — that is, the accumulation of edema

*Schroeder, H. A. Renal failure associated with low extracellular sodium chloride. *J. A. M. A.* **141**:117-124, 1949.

fluid in the center of the cell cords. This lesion is often seen in shock-like states and severe burns and with acute infections. There certainly was a considerable degree of adrenal damage, but I have no way of telling whether it was three days or three hours in duration.

The original diagnosis in relation to the heart was entirely correct. There was an old myocardial infarct of the left ventricle based on total occlusion of the left descending coronary artery. There was a mural thrombus in the ventricle, and another mural thrombus was found in the right auricle. The lung showed very severe congestion and edema and likewise showed three infarcts, which were somewhat anatomical curiosities in that all three were present in the central portions of the lung tissue and did not involve the pleural surfaces as forty-nine out of fifty pulmonary infarcts do. What the mechanism of such infarction is I do not know. There were reasonably fresh, nonadherent thrombi in the arteries bordering on each of these various areas of infarction.

DR. KRANES: Have any careful studies been made on the tubular epithelium in these patients?

DR. MALLORY: No; I do not believe so.

DR. KRANES: I tried, unsuccessfully, to find some reference to renal histology in these patients.

DR. MALLORY: I think it is quite possible that an elaborate study of the renal epithelium would show some degree of damage. For instance, if one has appropriately fixed material, loss of phosphatase gives evidence of minor functional injury when the epithelium as seen with any of the standard stains appears quite normal. I know of no such histochemical studies in this syndrome.

DR. S. M. MCCANN: Because we had considered this syndrome and we thought we had ruled it out, it seems pertinent to raise a few additional points.

I wish to say first that I believe the discussion by Dr. Kranes was extremely good. There were, however, several facts not brought out in the protocol that are pertinent. In the first place, before entry, the patient was on a diet without added salt and without ammonium chloride but with mercury injections every week. Secondly, the nonprotein nitrogen was normal on entry. Thirdly, the admission to the hospital from the Emergency Ward was prompted by severe nausea and vomiting subsequent to administration of 0.5 mg. of digitoxin and associated with frequent premature beats and runs of bigeminal rhythm. Fourthly, he continued to be nauseated and vomited an average of approximately 200 cc. a day for four days, and during this interval fluid intake by mouth was very poor. Fifthly, at the end of this period, the nonprotein nitrogen was 94 mg. per 100 cc., but the chloride of 92 milliequiv. per liter was only slightly below normal. Sixthly, at the time of extreme forcing of fluids the output rose concomitantly, and the chloride was 85 milliequiv. per liter at the end of this interval. Seventhly, a low-sodium syndrome was then suspected by Dr. J. D. Stoeckle, who administered 20 gm. of sodium chloride over the next three days. This was not associated with improvement — in fact, the patient developed increasing ankle edema and oliguria. Finally, even late in the course the patient got a definite though small diuresis from Mercuhydrin. Thus, it was believed that this syndrome was ruled out.

The low-sodium syndrome described by Schroeder is usually associated with sodium and chloride levels lower than any recorded in this patient, with oliguria (this patient's ouptut was never under 500 cc. and rose to a maximum of 2000 cc. on fluid therapy) and with improvement on massive sodium-chloride therapy. Improvement did not occur in this patient. The Ward Staff believed that the patient's uremia was precipitated by the nausea and vomiting associated with digitalis intoxication and kept going by the hypotension and associated poor renal blood flow in a patient with nephrosclerosis. What role the adrenal played I am not prepared to say.

DR. KRANES: The additional information supplied by Dr. McCann is helpful in giving us a clearer picture of this patient's clinical course, but does not necessarily exclude the possibility of a low-salt syndrome. Although it is true that most of Schroeder's patients had lower serum chloride concentrations than the patient under discussion, some did not. Furthermore, it seems quite certain that there is no critical sodium or chloride level at which these symptoms might be expected to occur, for we frequently encounter patients with astonishingly low levels of both in whom renal function is maintained quite adequately.

The fact that 20 gm. of salt, given over a three-day period, produced no improvement and, in fact, made the patient a bit worse has little relevance unless we know how much fluid was given during this time. If it were given in the form of isotonic sodium chloride, it could not be expected to remedy the suspected salt deficit. If given orally in the form of salt tablets, while at the same time intravenous glucose in water was being administered, — especially in any significant quantity, — the same result would ensue. It would be effective only if given in hypertonic form intravenously, or with fluids markedly restricted if given orally. The implication that this patient received adequate sodium chloride therapy is consequently open to serious question.

But even if we assume that an adequate amount of salt had been given, the failure to improve cannot be used as an argument against the syndrome under discussion. Not all of these patients can be saved or improved by proper amounts of salt. Schroeder states that "*Sometimes* this condition can be reversed by the intravenous injection of hypertonic sodium chloride solution in amounts

sufficient to restore electrolyte-water equilibrium." It has been the experience of others that the condition is not always reversible.

The determining factors are certainly still obscure. In the patient under discussion microscopical examination suggests that adrenocortical function may have been severely deranged. Given another patient with similar clinical findings, the administration of desoxycorticosterone acetate would merit serious consideration.

CASE 36332

Presentation of Case

First admission. A sixty-four-year-old woman was admitted to the hospital because of vaginal staining of one year's duration.

On physical examination there was a large, nodular, easily bleeding tumor almost completely replacing the uterine cervix and extending into the posterior vaginal wall and submucosally around the cervix onto the vaginal wall. There was definite thickening of the parametrial tissues about the cervix, mostly on the right, but the cervix and fundus were fairly movable. A rectal examination disclosed definite thickening and invasion of the right parametrial tissues, with some fixation. Blood and urine studies and a roentgenogram of the chest were negative. A biopsy of the cervical tumor was reported as squamous-cell carcinoma, Grade III. Subsequently, two 50-mg. radium needles were implanted in the cervical canal in a bomb casting giving a total of 2500 mg. hours. Treatment was temporarily interrupted three days later when the patient developed phlebitis of the left leg for which a bilateral superficial-femoral-vein interruption was done. Two days later a second radium implantation was carried out, giving a second total of 2500 mg. hours. The patient's course was uneventful and she was discharged four days later. During the next thirty-seven days she was given twenty-eight x-ray treatments that delivered a tumor dose of 5000 r into the middle of the pelvis.

Second admission (about two months after the termination of x-ray therapy). Except for a little diarrhea and superficial dermatitis, the patient felt well following the radiation therapy until one month before entry, when she began to have steady, mild, periumbilical pain. Bowel movements continued to be regular, and no melena was noted. Four days before admission the patient began to vomit everything she ate, although she was not especially nauseated. She passed some gas on the first day, but had had no bowel movements and had not passed any gas since that time. The periumbilical pain became intensified with the onset of vomiting and was somewhat crampy but was never extremely severe. Physical examination showed little more than before except for a protuberant abdomen and a slightly tender area just below the umbilicus. A pelvic examination showed partial stenosis of the upper vagina due to adhesions and scarring. Above this the cervical remnant was nodular and irregular but without fixation. A 5-cm. segment of gangrenous lower ileum near the ileocecal valve was found adherent to the uterus and omentum and was resected, and an ileotransverse colostomy performed. The course was not eventful, and she was discharged asymptomatic on the nineteenth postoperative day. The pathological report on the segment of ileum was radiation necrosis and fibrosis.

Third admission (six months later). In the interval the patient had remained asymptomatic. She had been followed monthly in the tumor clinic, where vaginal smears for cytologic examinations were consistently negative. Five days before entry she developed vomiting, chills and fever and right-upper-quadrant pain radiating through to the back. These symptoms persisted. On physical examination there was mild icterus. The abdomen was flat, soft and slightly tender over a rather wide area involving epigastrium and both right and left upper quadrants. No masses were palpable. The temperature was 101°F. and the pulse 120. The urine gave a + test for albumin and the sediment contained 3 to 5 white cells per high-power field. The blood hemoglobin was 12.8 gm., the white count 5400. The serum van den Bergh was 0.7 mg. per 100 cc. direct, 3.4 mg. per 100 cc. total, and the amylase 82 units per 100 cc. Other blood chemical and liver-function studies were normal. One stool guaiac test was ++++, and a second stool was grossly bloody with clots. In the hospital the patient's symptoms gradually subsided and she became afebrile. A consultant found no evidence of recurrent or residual tumor in the pelvis, and sigmoidoscopic examination showed diffuse scarring and telangiectasis of the mucosa but no other lesions. Plain films of the abdomen and a barium enema were normal, the latter showing a well functioning, transverse ileocolostomy. A Graham test did not demonstrate any shadow representing gall bladder. On the fourteenth hospital day a cholecystectomy, choledochostomy and exploration of the common duct were performed. The common duct was negative for calculi or other disease. The abdominal organs were palpated and found negative for any evidence of tumor except for an iliac lymph node, 1 cm. in diameter, which was not removed. The pathological report was subacute and chronic cholecystitis and cholelithiasis. The patient was discharged on the twelfth postoperative day.

Final admission (about nine months later). After discharge from the hospital the patient experienced increasing bowel difficulty, characterized by tenseness, diarrhea and occasionally bloody stools. She also complained of lack of appetite but actually she had gained 10 to 15 pounds in weight since the previous admission. At the time of her last tumor

clinic visit, it was believed that symptoms had become of sufficient degree to warrant further study, and admission to the hospital was advised.

Physical examination showed a well developed and well nourished, elderly woman in no acute distress. The heart revealed a Grade I systolic murmur at the base, and the lungs were clear. Examination of the abdomen was negative for tenderness or masses. The vagina was completely stenotic just inside the introitus. Rectal examination showed thickening in the cervical region but no definite evidence of recurrent tumor.

FIGURE 1.

A urine specimen was normal. The blood hemoglobin was 10.5 gm., and the white-cell count 12,000. The nonprotein nitrogen was 25 mg. per 100 cc. A guaiac test on the stool was +++.

In the hospital the patient's condition remained unchanged. A cystocopic examination was negative. A sigmoidoscopic examination showed rigidity of the wall and thickened grayish-pink, granular mucous menbrane, with scattered, blotchy, red areas. These areas bled easily on swabbing, and the bowel lumen was narrowed. A barium enema showed passage of dye into the large bowel up to the cecum, where obstruction was encountered. The cecum never filled out satisfactorily in contour (Fig. 1), and there was a suggestive mass with evidence of shelf formation measuring about 6 cm. in greatest diameter. There was some irregularity over the sigmoid colon but no evidence of a filling defect or ulceration. A roentgenogram of the chest was normal. A plain film of the abdomen showed both kidneys to be normal in size, shape and position. The calyxes, kidney pelvis and ureter on the right side appeared normal. On the left side there was slight displacement of the kidney pelvis, which was interpreted as a normal variation. A retrograde pyelogram showed adequate filling of the left calyxes and visualized the deformity previously described on the intravenous pyelogram. A second barium enema confirmed the presence of the previously described cecal defect. Urine cultures were negative.

On the seventh hospital day an operation was performed.

DIFFERENTIAL DIAGNOSIS

DR. GRANTLEY W. TAYLOR*: There is enough information given about this case so that I could talk most of the day about it. However, I shall confine myself to a discussion of the final problem and its relation to the bowel. The patient had had a rather advanced carcinoma of the cervix — certainly stage II and possible stage III — for which she was given radiation that apparently resulted in cure. She was followed with repeated vaginal smears. Dr. J. V. Meigs and Ruth Graham, in the Vincent Laboratory, believe that if the smear remains negative for some time after treatment, it is a definite indication that the neoplastic process is under control. At any rate there were no further positive smears in the case under discussion, and at the time of the gall-bladder operation there was nothing to suggest the dissemination of the cancer intra-abdominally except possibly the lymph node, 1 cm. in diameter, in the iliac region.

It should be noted that the patient had radiation damage for which an ileotransverse colostomy was done. I think one should stress the fact that radical radiation is not without hazard. Destructive change in the bowel going on to gangrene, intestinal obstruction or perforation is a well recognized possible complication of massive radiation therapy. Morris and Meigs[1] have recently presented a résumé of their experiences in the Massachusetts General Hospital, Pondville Hospital and Palmer Memorial Hospital with x-ray treatment for carcinoma of the cervix and the considerable amount of damage following it.

Before going into this any further, I should like to see the x-ray films of the colon taken at the time of the last admission.

DR. JOSEPH HANELIN: The first set of colon films were taken after the ileotransverse colostomy.

*Visiting surgeon, Massachusetts General Hospital.

They fail to show any filling of the bowel beyond the region of the splenic flexure. The anastomosis of the ileum and transverse colon is visible at the proximal portion of the transverse colon. The last set of films of the colon demonstrate smooth narrowing in the region of the rectum and sigmoid. There is no other evidence of abnormality until we reach the area of the cecum. The cecum itself is situated rather low and extends into the true pelvis; there is a filling defect (Fig. 1), which is approximately 7 by 5 cm., principally along the medial aspect. Shelf formation is present proximally. It is most suggestive of deformity by extrinsic pressure. The shelving may be due either to adherence of a mass to the bowel or to actual invasion of the bowel wall. The intravenous pyelogram shows minimal deformity of the left calyxes, which is probably due to secondary contraction of the kidney.

DR. TAYLOR: There was evidence of an acute inflammatory process, with chills, fever, vomiting and right-upper-quadrant pain. The only thing against a gall-bladder condition was the positive guaiac reaction on the stool. The patient was explored, and definite evidence was found of inflammation of the gall-bladder that was confirmed by the pathologist. However, I cannot believe that the gall-bladder problem was anything but incidental. One thing I should like to draw attention to is that at the time of the cholecystectomy, the abdomen was carefully palpated by the surgeon, and the organs were described as essentially normal. I have always been a little skeptical, being a surgeon myself, about how much it is worth to pass a hand around the abdomen and say this is normal, that is normal and the other thing is normal, especially when it is not always possible to make a diagnosis grossly.

Now I am going to mention two conditions. This patient had radiation damage of the intestine as shown by the laparotomy for a resection of a gangrenous area. I can say that she had ulcerative colitis; it was not an ulcerative colitis of the agnogenic, idiopathic type but secondary to radiation. Also, she had terminal ileitis. Now those are both quite serious diseases. The presence of an ulcerative process involving the colon and the terminal ileum puts a person in a precarious situation in regard to lower-bowel function. Was the cecum also included in the radiation therapy? I think it was because the terminal ileum right up to the ileocecal valve was the area that was gangrenous, the cecum was low in the pelvis, and the disease seemed to be primarily in the region of the cecum. What was causing the trouble there? First and foremost I must consider that it may all have been due to a late radiation change in that area. Radiation damage to the bowel may be present for many years afterward.

Had the patient metastases from the cervix involving the region of the cecum? It seems to me rather unlikely. I think that a metastatic carcinoma would have been suspected either on gross palpation or at the time of the laparotomy. Had she an ovarian metastasis with adhesions to that region of the cecum? Again, I think not, and for the same reason. Had she a new cancer of the cecum entirely independent of the process in the pelvis, or had she a carcinoma in a little stump of terminal ileum that was left when it was transected at the time of resection of the gangrenous bowel? I should like to ask Dr. Mallory whether he has ever seen evidence of carcinoma induced by excessive radiation in the bowel? It is very common to see carcinoma originating in an area of skin following excessively heavy radiation. Also, osteogenic sarcoma may arise in bone that has been heavily radiated. There have been cases of fibrosarcoma originating in soft tissue subjected to radiation. Experimentally, gall-bladder and thyroid carcinoma have been induced by radiation of the tissue. Smith and Bowden,[2] from the Memorial Hospital, wrote a paper on the question of whether carcinoma of the endometrium may be induced by late radiation changes in the endometrial tissue and concluded that it probably was in some patients. I am not aware of any case of bowel damage caused by radiation that went on to the development of cancer. However, I think that we must realize that we are using an agent that may under certain circumstances be carcinogenic.

DR. TRACY B. MALLORY: I cannot recall that we have had any here.

DR. TAYLOR: I do not think that we have.

Finally, there is another condition — a chronic inflammatory process. Whenever I am confronted with a mass involving the cecum on gross examination I cannot be sure whether I am looking at a primary carcinoma or whether I am looking at a chronic inflammatory process. There have been a number of resections for carcinoma of the right bowel that on pathological examination proved to

be a chronic appendiceal suppurative process, tuberculosis of the cecum or some other nonspecific type of inflammation in that region.

I come down to the probable disease that accounts for these x-ray findings and symptomatology — disease of the cecum. Was it due purely to radiation? Was it chronic inflammation? Was it an extension of the cervical carcinoma or a new and unrelated neoplasm in the cecum? If the last, might it have been secondary to the radiation to which the bowel was subjected? I do not believe I can go very much farther than that in setting forth the possibilities. The shelf formation seems to me much more in keeping with an intrinsic than an extrinsic bowel disease. On the other hand only one side of the cecum was apparently involved, which is very much against an intrinsic disease. If I have to come out flat footedly and say that I favor one or the other I would say that the patient had an independent primary neoplasm, probably of the cecum. I do not think we can rule out an implication of what was left of the terminal ileum distal to the point of resection.

Clinical Diagnosis

Radiation enteritis.

Dr. Taylor's Diagnoses

Carcinoma of cecum.
Colitis and ileitis secondary to radiation.

Anatomical Diagnoses

Adenocarcinoma of cecum.
Chronic radiation enteritis.

Pathological Discussion

Dr. Mallory: This patient was explored, and a tumor was found in the cecum. That and the ascending colon were resected practically up to the point of the previous ileocolostomy. The tumor was adherent to one loop of small bowel, which could not readily be dissected free and was likewise resected with the cecum. The specimen received in the laboratory showed obvious primary carcinoma of the cecum surrounding the orifice of the ileocecal valve. It was also noted that the wall of the cecum a considerable distance from the tumor was thickened, in some spots as much as 1 cm., and densely fibrotic. It was believed that this represented more of the radiation enteritis in chronic form that, in its acute form, had produced incipient gangrene of the ileum. This was a carcinoma of the cecum developing in an area that showed very marked radiation changes and constituted very suggestive evidence that the radiation may have been a contributing factor in the formation of the tumor.

Dr. Taylor: Do you think that there must be a long lapse of time between the radiation injury and the development of carcinoma to justify the assumption that it is the etiologic factor? I note, for instance, that Smith and Bowden[2] stated that ten years ought to elapse after radiation of the uterus for artificial menopause to be sure that a cancer was not originally the cause of the menorrhagia or whatever other condition was present. I do not think it is necessary to assume such a long interval.

Dr. Mallory: I think it very probable that the effect would be produced much more quickly in one person than in another. There is a clear analogy in cases of carcinoma that develop in the fistulous tracts of draining osteomyelitis. We have seen them develop in as short a period as three years, and in other cases the interval may be ten or fifteen years; the average is close to ten years.

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FINANCING MEDICAL EDUCATION

TRADITIONALLY, medicine has never been a lucrative profession. To be sure, from time to time individual physicians have achieved great popularity and wealth, but these were exceptional cases, the average practitioner eking out a barely respectable living from his work. The attitude of the community toward the local doctor has been inevitably colored by an appreciation of how little material reward he received for the services that he rendered.

The last twenty-five years have seen a marked increase in the average net income of physicians in the United States, which has made the doctor one of the more prosperous members of his community. There has been a concomitant increase in the cost of medical education, and although tuition rates have been advanced, the relative amount that the future doctor pays toward the cost of his professional education has decreased to the point where it is being paid for largely by others. The report of the Council on Medical Education and Hospitals of the American Medical Association for the academic year 1948–49 indicated that tuition supplied only 22.8 per cent of the cost of medical education. In other words, more than three quarters of the cost of his medical education was given to the prospective physician free of charge. In the state universities, the excess of cost of instruction over tuition is taken from the taxpayer's pocket, and, to date, there have been no signs of serious objection on the part of the citizens. However, the private schools whose revenues derive from endowment income, voluntary gifts and operational income have found it utterly impossible to make ends meet. Some of the finest private medical schools in the country are virtually bankrupt, and one or two are in imminent danger of closing. Those who are trying to raise funds from lay sources to rescue medical education are confronted with a somewhat awkward contrast between the relative prosperity of the profession and the poverty of the schools that provided them with their earning power.

Why, it may be asked, should not the doctor pay for his own education in toto? Although tuition costs are at a maximum level in most medical schools, might it not be possible to defer payment of some, and perhaps most, of the tuition until the period of earnings is high? In that way, might not full tuition costs be finally recovered by the schools? Such a scheme would necessarily have to be set in motion simultaneously by a number of different schools. This would involve considerable financing. The doctor has generally been rated as a good credit risk. What more appropriate contribution could the life-insurance companies of the land make to the health of the country and to their own self-interest than to underwrite a revolving loan fund to make medical education pay its own way? Loans could be protected by life-insurance policies, and interest rates kept low until the educational period was over. Such loans could be discounted and paid over to the universities immediately. From the point of view of the recipient, the repayment of the loan would probably be deductible from income tax as an expense of professional education.

If the organized medical profession, as represented by the American Medical Association, is going to continue to oppose federal aid to medical education, is it willing to accept the financial responsibility of the individual physician for his own education? If so, some such scheme of long-term financing might solve the dilemma in keeping with the traditions of the system of free enterprise. In fact, even governmental financing under such terms might be acceptable.

REPORT ON THE SCREENING CLINIC

IT MUST be apparent that the so-called multiphasic screening clinic in which an individual is considered as a whole, although with particular emphasis placed on especially vulnerable systems, is superior to any variety of specialized clinics.

This opinion is substantiated in the "Preliminary Report on the Health Protection Clinic" prepared by Ryder and Getting for presentation at the annual session of the Massachusetts Medical Society and published elsewhere in this issue of the *Journal.* Since "the composite benefits of all acceptable screening technics are applied at a single visit" it is apparent not only that money and time are saved but that the patient is spared the false sense of security that comes from an impressive but limited examination.

This clinic, which has suspended operations after the six months' original run that was planned for it, was authorized by the Council of the Massachusetts Medical Society in May, 1949, at which time a committee was empowered to co-operate in the establishment of not more than five such clinics. In order that at least one should be in fact put into operation, funds were made available by the Public Health Service and the Massachusetts Department of Public Health, and contributions were received from the Massachusetts Heart Association and the Massachusetts Division of the American Cancer Society.

The establishment of the clinic last December at the Joseph H. Pratt Diagnostic Hospital of the New England Medical Center was aided and approved by the Subcommittee on Pilot Clinics of the Committee on Public Health of the Massachusetts Medical Society, which gave freely of its advice and exhibited a genuine interest in the venture. In this relation it must be emphasized that, from the point of view of the medical profession, the screening service that the clinic provided was incidental to its value as a research project to test the "effectiveness, specificity and fallibility of various screening methods and tests," as well as their cost.

In six months' time, approximately 2600 patients have been "screened" at a total cost of $35,000, or about $14 per patient, and it is believed that this cost can be reduced to $5, with a reduction in the number of tests and a shortening of the physical examination. The greatest benefit of the procedure, that of the discovery of disease that can be cured or ameliorated, can be statistically appraised; it is more difficult to put a price on the satisfaction that a person may derive from knowing that at a given moment he is apparently free from any serious threat to his health.

The continuance of this clinic and the establishment of additional ones up to a present limit of five must depend first on the availability of funds. Their expansion should also depend on a final decision regarding both their value in terms of health protection and their acceptability as part of the changing social and economic aspects of medical practice. The final criterion in the long run will be the greatest good to the greatest number of people. From this principle there should be no departure.

THE AMHERST CONFERENCE

THE Committee on Postgraduate Medical Education of the Massachusetts Medical Society in conjunction with the Massachusetts Department of Public Health, will conduct a teaching conference at the University of Massachusetts, in Amherst, on September 13, 14 and 15. The intensive course offered will include, in addition to more orthodox subjects, practical instruction in the medicine and emergency treatment required by atomic warfare.

The increased service offered by such a course is in line with the enviable performance of this com-

mittee since it started its educational program five years ago. During the past year its circuit-riding pedagogues have conducted 43 exercises in 12 far-flung areas of the Commonwealth, and in addition 61 lectures, this year held at the Boston Medical Library, have made up the famed "Sanders College" curriculum.

The Conference at Amherst is warranted — in fact, necessitated — by the past and continuing popularity of the instruction offered by the Committee. An additional reason for the conference is the desire of the Committee to co-operate, through the Massachusetts Chapter, with the American Academy of General Practice, which requires its members to take fifty hours of postgraduate instruction each year.

On, then, to Amherst: "Westward the course of Empire takes its way"!

DOCTOR OF SCIENCE

A SIGNAL tribute was paid to a leader of the medical profession in Massachusetts on Commencement Day, June 22, when Harvard University conferred the honorary degree of doctor of science on Dr. Paul D. White, of Boston. The recipient of many similar honors both in this country and abroad, Dr. White was one of ten leading men in public life, natural science and education to be awarded honorary degrees by the University this year.

His associates here and elsewhere — indeed, all who have observed his achievements in the practice and teaching of cardiology — will see a fitting description of Dr. White in the citation that accompanied the degree: "A physician who has successfully combined practice, teaching and research; an investigator distinguished for his studies of the heart."

Two doctors, in Virginia, have been disgracing themselves by attempting to shoot one another; unfortunately, the balls did not prove mortal to either.

Boston M. & S. J., *August 14, 1850*

OBITUARY

FRED BATES LUND
1865–1950

Dr. Fred Bates Lund was born at Concord, New Hampshire, on January 4, 1865, the son of Charles Carroll Lund and Lydia French, each of long New England heritage and both college graduates.

Dr. Lund prepared for college at Phillips Andover Academy. After graduation from Harvard College, summa cum laude, in 1888, he entered the Harvard Medical School, receiving the degrees of M.D., cum laude, and A.M. in 1892. His internship was served at the Massachusetts General Hospital.

As was the case with many Boston surgeons of that era, Dr. Lund's early postgraduate study centered in the anatomical laboratories of the Harvard Medical School, where he taught as assistant in anatomy from 1895 to 1899. Appointed to the staff of the Boston City Hospital in 1895, he rose through the various grades to that of surgeon-in-chief, retiring in 1926, when he was made consulting surgeon. From 1926 to 1935, he was surgeon-in-chief at the Carney Hospital.

Dr. Lund was one of the last "anatomical surgeons" of Boston. To that school, perfection as an anatomist was a *sine qua non* for a successful surgical career. Of gross pathology they had considerable knowledge; of physiological principles, as applied to surgery, their concept was limited. Anesthesia was restricted in types and scope and anesthetists, as specialists, were few. In retrospect, those of us who realize these handicaps are much impressed at the favorable percentage of Dr. Lund's surgical endeavors. In the operating room he was an exacting but fair master, and for this guidance his interns have been most grateful. At the bedside, his examinations were rapid but thorough.

His qualities as a clinical teacher were recognized by the Harvard Medical School. where he held appointments in the Department of Surgery from 1901 to 1918.

Dr. Lund's contributions to medical literature numbered over one hundred papers. He was much honored by the medical profession, having been president of the Boston Surgical Society, the New England Surgical Society, the American Congress of Surgeons, the Society of Clinical Surgery and the American Surgical Association. His memberships also included the American Gastroenterological Society, Massachusetts Medical Society and the American Medical Association.

In 1915, Dr. Lund accompanied the Harvard University Unit to France, serving with the British Base Hospital No. 22. Later he organized Base Hospital No. 51, A.U.S., serving as surgeon-in-chief with the rank of lieutenant colonel until an eye injury prevented him from accompanying this unit overseas.

Long a student of Latin and Greek, Dr. Lund indulged in these classics as a hobby. From such study it was natural that he became a member of the American Philological Association and the New England Classical Association. He was president of the Boston Classical Club. In 1936 he published a volume entitled "Greek Medicine."

Dr. Lund's love of outdoor life took him on many hunting and fishing trips to Maine, New Hampshire and New Brunswick. Throughout his busy years in surgery he sought relaxation in the goodfellowship of the Tavern Club.

In 1893, he married Miss Zoe M. Griffing, of Lexington. Besides his widow, Dr. Lund is survived by five children, among whom is Dr. Charles C. Lund, of Boston. He also leaves twelve grandchildren.

I. J. W.

MASSACHUSETTS MEDICAL SOCIETY

DEATHS

BOYD — Francis P. Boyd, M.D., of Springfield, died on May 11. He was in his sixty-fifth year.

Dr. Boyd received his degree from Tufts College Medical School in 1911. He was a member of the staffs of Wing Memorial Hospital, Palmer, and Mercy Hospital. He was a member of the New England Obstetrical and Gynecological Society and a fellow of the American Medical Association.

His widow and several children survive.

CONNELL — Arthur I. Connell, M.D., of Fall River, died on July 18. He was in his eighty-sixth year.

Dr. Connell received his degree from Harvard Medical School in 1890. He was a fellow of the American Medical Association.

A sister, a nephew and a niece survive.

DRAPER — Alexis L. Draper, M.D., of Dorchester, died on July 15. He was in his seventy-eighth year.

Dr. Draper received his degree from University of Pennsylvania School of Medicine in 1896. He was a fellow of the American Medical Association.

His widow, two daughters and six grandchildren survive.

LIBBY — Mildred A. Libby, M.D., of Holden, died on May 2. She was in her seventy-fifth year.

Dr. Libby received her degree from Woman's Medical College of Pennsylvania in 1898. She was formerly senior physician at the Wrentham State School.

A sister survives.

MURPHY — Joseph W. P. Murphy, M.D., of Peabody, died on July 27. He was in his sixty-first year.

Dr. Murphy received his degree from Tufts College Medical School in 1914. He had been medical examiner for the Peabody–Danvers–Middleton–Lynnfield district for the past twenty years.

His widow, a daughter and a brother survive.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

PRELIMINARY REPORT ON THE HEALTH PROTECTION CLINIC*

CLAIRE F. RYDER, M.D.,† AND
VLADO A. GETTING, M.D.‡

The concept of multiphasic screening is not one person's idea, nor a new one, but has evolved logically during recent years from the discovery that individual screening clinics, in which the presence or absence of only one or two diseases is determined, are often costly, may lead to a feeling of false security in the patients screened and take too much time. One of the inherent errors of the present screening program is that the person who has been screened for heart disease, diabetes or cancer may believe (often erroneously) that he is free from other diseases. In addition, in screening for a single disease the health-education program expenses, personnel and other costs may be prohibitive. It has been found that in cancer-detection centers, for example, the cost of finding a single case of cancer may reach $20,000.

Through multiple or multiphasic screening clinics, on the other hand, the composite benefits of all acceptable screening technics are applied at a single visit. The persons examined are screened for the presence of the major conditions that may lead to serious protracted illness or disability. Through early detection of such conditions as heart disease, hypertension, diabetes, cancer, tuberculosis and nephritis, patients are referred to their family physicians for final diagnosis and treatment. By cutting down the incidence of complications and of long-term care in hospitals or at home, and the serious loss of earning capacity, a multiphasic screening clinic is good preventive medicine.

In May, 1949, the Council of the Massachusetts Medical Society voted at its annual meeting to establish five pilot multiphasic clinics; at the same time it set up and empowered a committee composed of one member from each of the eighteen districts, to act in accordance with the plans proposed by the Massachusetts Department of Public Health for a screening program in the Commonwealth.

Soon afterward a co-operating grant was received from the Public Health Service, and funds were likewise made available from the Massachusetts Department of Public Health for an initial multiphasic clinic. Two voluntary agencies, the Massachusetts Heart Association and the American Cancer Society (Massachusetts Division), also contributed to the support of this first venture. With the development of the plan by the committee of the Massachusetts Medical Society, the New England Center and

*Presented at the annual meeting of the Massachusetts Medical Society, Boston, May 17, 1950.

†Administrator, Health Protection Clinic, Massachusetts Department of Public Health.

‡Commissioner, Massachusetts Department of Public Health.

Joseph H. Pratt Diagnostic Hospitals in Boston became the first location for the clinic.

During the first week in December, a trial run of the clinic was held in which 100 of the Department's own personnel were screened. Finally, on January 3, 1950, the Health Protection Clinic was opened to the public. There was a literally overwhelming response to the single news release announcing the clinic. The telephone system became disrupted from the enormous influx of calls. People also called in person, and flooded the office with letters. To the joy of the telephone company, the instrument was disconnected after only three days, and news releases were sent out announcing that all further requests for appointments must be made by mail. Yet the applications still arrived in such quantities that twice as many requests were received as could be granted for appointments.

Purpose

The purpose of the Health Protection Clinic is multifold. In the first place it serves as a screening clinic to detect suspicion of disease and subsequently to refer the screened persons to their family physicians for final diagnosis and treatment. Secondly, the clinic serves as a research project to determine a pattern for multiphasic screening programs and to evaluate the effectiveness, specificity and fallibility of various screening methods and tests. Thirdly, an evaluation is being made of screening procedures from the point of view of cost, to determine types of clinics that may be set up according to the availability of facilities and funds. Finally, it is the intent of the clinic to motivate people, through health education, not only to have annual physical checkups but also to see their doctors immediately, should any symptoms of disease arise.

Diseases Screened

The diseases for which screening methods have been used in the past, and for which the Health Protection Clinic screens a person, include nine main categories: heart disease, hypertension, diabetes, tuberculosis, cancer, syphilis, nephritis, vision and hearing defects, and nutritional status (including overweight and underweight).

Methods of Approach

In general, the approach to the problem of screening the diseases named above falls into three categories — that is, history, clinical procedures and physical examination.

History

The history used in the Health Protection Clinic is adapted from the Cornell Medical Index. It is called a "Health Protection Self-Screener," which the subject receives and fills out at home prior to his visit to the clinic. It consists of 222 questions, covering not only all the important signs and symptoms of the diseases screened but also a nutritional history, a psychosomatic evaluation and a check on health habits.

The person screened returns the questionnaire to the clinic at the time of his visit, where it is reviewed by a worker trained in social service known as the history taker. Any unanswered questions are explained, and answers obtained, with elaboration of certain problems such as family history of disease and previous diagnoses made by the family physician, all for the purpose of assisting the examining physician. The history taker clarifies certain symptoms of disease for the clinic's examining physician, who later in the clinic session makes the examination, goes over the positive answers on the history and records on the special clinic card any pertinent facts that he may have elicited.

Clinical Procedures

The following clinical procedures are carried out in every case. A venous blood sample is drawn, on which a Hinton test is done, and also a hemoglobin determination by photoelectric colorimeter, and a sugar screening by the Wilkerson–Heftman method. Next, a urine specimen is obtained, and presence of sugar determined by Clinitest tablet and of albumin by sulfosalicylic acid granule. A hearing test is then conducted by means of a Pure-Tone Audiometer. A vision test follows, for which a revised screening method has been developed, using the Bausch and Lomb Ortho-Rater. Next, the person being examined disrobes, and is seen by the clinic nurse, who takes readings of temperature, pulse, respirations, blood pressure, height and weight. A 70-mm. photofluorographic x-ray film is then taken. In the trial run of the clinic, it was found necessary to have the persons being screened disrobe for the x-ray examination, for technical reasons; the x-ray study at present is done after the other clinical tests when the person being screened is ready for the physical examination.

Physical Examination

The physical examination is performed by clinic physicians who are in active practice and who are, for the most part, eligible for board examination in internal medicine. The examination, including a brief interview, averages about twenty minutes. It includes routine check of heart, chest, neck, abdomen and extremities, and rectal examinations for all. Pelvic examinations are done on all married women, and Papanicolaou smears are taken if signs or symptoms indicate the possibility of cancer of the uterus. Since rectal examinations are done on every patient, testing for occult blood in the stool by the Hematest method has recently been added to the clinic procedures. It seems from the above that, technically speaking, the Health Protection Clinic is not one devoted entirely to screening, since history and physical examination are so com-

plete. It was the intent of the committee of the Massachusetts Medical Society to evaluate screening procedures and to determine whether or not the physical examination revealed disease that was missed by the history or clinical tests. By comparison of the results of these three methods of approach, it may be possible eventually to limit the physical examination to areas where, at present, clinical tests are not available for the screening of disease, or to eliminate it entirely.

Screening Levels

The screening levels chosen to determine whether or not a person should be referred to his family physician for final diagnosis and treatment are as follows:

Hemoglobin. For women, 10 gm. per 100 cc. or less; for men, 11 gm. per 100 cc. or less.

Blood sugar. All positive blood sugar specimens are sent to a Public Health Service laboratory for an actual glucose determination. All tests are done by Nelson–True Glucose Method, which is about 20 mg. per 100 cc. below Folin–Wu determination. Above 180 mg. per 100 cc. is considered an indication for referral. Below 180 mg. per 100 cc. a glucose tolerance test is done.

Hearing. Unilateral or bilateral drop below 30 decibels at 500, 1000 and 2000 cycles.

Vision. Less than 20/40 vision, near or far, with either or both eyes.

Weight. Twenty per cent above or below ideal weight.

Blood pressure. Systolic pressure of 150 or above; diastolic, 90 or above.

X-ray film. Positive findings on the 70-mm. x-ray film, unless obviously insignificant, are checked by means of a large chest plate (14 by 17 inches).

Operation of the Clinic

At present four clinic sessions are held a week — three in the evening from 6:00 to 9:30, and one on Saturday afternoon from 2:00 to 5:30. At each session between 25 and 30 persons are seen, or in other words, 100 to 120 a week. The first clinic was a limited project, having ended on June 30, at which time approximately 2600 persons had been seen. Appointments are made at five-minute intervals; it requires approximately an hour for the person being screened to go through the entire clinic.

After his visit, an analysis is made of all the findings, and letters are sent to both the family physician and the person examined indicating whether or not there is a suspicion of disease. The physician, in addition to the letter giving all the positive findings, receives a copy of the self-screener history that the person filled out and brought to the clinic. A patient who is referred to his family physician is told only that there is a suspicion of disease for which he should consult his physician immediately. However, when the reason for referral is obesity or vision or hearing defects, alone, the patient is told that this is the reason for referral. The nature of results indicating any other condition is revealed to the family physician only. The physician is asked to return a special card on which he is to indicate the final diagnosis, either after he has seen the patient or if he has been aware of the conditions present. If, after a month, no word is received from the physician, the clinic nurse calls him, to determine whether or not the patient has seen him. A social-service worker then calls upon all patients who have not been to see the family physician.

Personnel

The present Health Protection Clinic, operating four times weekly, employs 4 examining physicians for each clinic; a medical social worker, not only as history taker but also as follow-up case worker; 2 clerks, 1 acting as receptionist at the clinic, the other performing secretarial duties during nonclinic hours, pertaining to referral forms and other records; 2 clinic nurses, 1 who takes the blood pressures and height and weight data, and a second who is responsible for the operation of the clinic, seeing that persons being screened are directed to the proper channels, and assisting the physicians when necessary. One of these nurses, in addition, is working part time on the follow-up study of patients. There are 3 laboratory technicians to do the laboratory tests on blood and urine, two medical technicians to operate the vision and hearing tests and 1 x-ray technician to take and process the 70-mm. photofluorographic x-ray film, as well as any large x-ray films that are required. In central administration, the staff includes the administrator of the program, an assistant biometrician, a senior statistical clerk and a stenographer.

Budget

The budget, including statistical evaluation and follow-up study, will reach about $35,000 for this six-month period at the New England Center and Joseph H. Pratt Diagnostic Hospitals. Of this amount approximately $16,000 has been made available by the Public Health Service, and grants of $1250 each have been made by the Massachusetts Heart Association and the American Cancer Society. The remaining $16,500 has come from the Massachusetts Department of Public Health. Roughly, the total cost per person seen in the clinic is estimated at about $14. By reducing the number of tests needed, and by shortening the physical examination, it is hoped that future clinics will be more economical to run, so that the final cost will be nearer to $5 than the present $14.

Results

To date, over 2000 people have been seen in the clinic; of these about 1500 records have been checked and analyzed, and the patients referred who have shown signs suggestive of disease. Approximately half these records have been evaluated, with the following results: of 753 persons screened 310 were referred for conditions previously unknown or not under treatment by the family physician; 449 defects were found that were previously unknown or untreated.

Obesity

The persons who are more than 20 per cent above the ideal weight outnumbered by far all other conditions, 136 cases of obesity being found.

Hypertension

Fifty-six cases of hypertension were discovered at the clinic.

Heart Disease

Of a total of 58 cases of heart disease, the breakdown included 7 cases of rheumatic heart, 18 cases of hypertensive heart and 33 cases of other types of heart disease. This last group included, for the most part, angina and coronary-artery disease, but there were, in addition, 2 cases each of congenital and syphilitic heart disease.

Vision Defect

Eighty-eight cases of vision defects were found, in which the patient either had no glasses or had not had refraction within the past year.

Hearing Defect

Forty-nine cases of hearing defects were found.

Diabetes

Fourteen cases of diabetes were discovered that were previously unrecognized, or if recognized, were not under treatment.

Anemia

The eleven cases of anemia were not classified for type or etiology.

Tuberculosis

Most of the 7 cases of tuberculosis were in early stages. One patient, in fact, had had a negative x-ray examination two months before reporting to the clinic. X-ray examination at the clinic was positive, and two months later the first symptom of the disease developed, with tuberculous pleurisy and effusion.

Syphilis

Surprisingly few cases of syphilis were found, with only 2 definitely proved and 1 still in doubt.

Cancer

Twenty-seven patients with lesions suspected of being cancer were referred to the family physician. Subsequent follow-up study by the staff of the clinic has revealed that, according to final diagnosis of the referral physician, there were 2 proved cancers, both of which were metastatic, 1 in the lung (primary site unknown), and 1 in the mediastinum from a hypernephroma. The remainder of the lesions were proved to be either precancerous or benign, and included 2 cases of rectal polyps, 2 cysts of the breast and 1 precancerous skin lesion.

Future Clinics

The final approval of the Massachusetts Medical Society provided for the establishment of not more than five such pilot clinics. Subsequently, up to the maximum of five could be planned — for example, one in a small community hospital (outpatient department), one in a large urban health center and one in a small community health center.

Under consideration at present is the establishment of a mobile unit that could carry from town to town the necessary equipment, supplies and personnel for multiphasic screening. It is also anticipated that a research clinic may be developed for the screening of school children.

NOTICES

ANNOUNCEMENTS

Dr. Seth C. Crocker announces the opening of his office for the practice of internal medicine at 184 School Street, Milton.

Dr. Seymour R. Shalek announces the opening of his office for the practice of diagnostic and therapeutic radiology at 520 Beacon Street, Boston.

AMERICAN TRUDEAU SOCIETY

The annual meeting of the Eastern Section of the American Trudeau Society will be held in Baltimore, Maryland, on November 10.

Dr. Hugh Whitehead, of Baltimore, is chairman of the Committee on Arrangements.

GRANTS FOR ENVIRONMENTAL CANCER RESEARCH

The Committee on Growth of the National Research Council, adviser for research to the American Cancer Society, announces the formation of a panel on environmental cancer with the following membership: Dr. Willard Machle, Chairman, Dr. Francis Heyroth, Dr. George H. Gehrmann, Dr. Herman Lisco and Dr. Norton Nelson.

The panel will review applications for grants in support of research in these areas. These applications, as with others submitted to the Committee on Growth, will be received until October 1.

Communications regarding grants may be addressed to the Executive Secretary, Committee on Growth, National Research Council, 2101 Constitution Avenue, N. W., Washington 25, D. C.

(*Notices concluded on page xi*)

NOTICES (*Concluded from page 280*)

SOCIETY MEETINGS AND CONFERENCES

JANUARY 9–DECEMBER 1. Laboratory Courses at Communicable Disease Center, Atlanta, Georgia. Page 950, issue of December 8.

AUGUST 21–26. International Society of Hematology. Page 888, issue of December 1.

AUGUST 28–SEPTEMBER 1. American Congress of Physical Medicine. Page 428, issue of March 16.

AUGUST 31–SEPTEMBER 7. World Federation for Mental Health. Page 306, issue of February 23.

SEPTEMBER 3–9. International Heart Congress. Page 160, issue of January 26.

SEPTEMBER 6–May 2. Hampshire District Medical Society. Page 170, issue of July 27.

SEPTEMBER 7–9. All-Austrian Congress of Physicians. Page 994, issue of June 22.

SEPTEMBER 14. Progress in the Management of Hand Injuries. Dr. Henry E. Marble. Pentucket Association of Physicians. 8:30 p.m. Haverhill.

SEPTEMBER 18–27. International Congress of Psychiatry. Page 240, issue of August 10.

SEPTEMBER 26–29. American Roentgen Ray Society. Page 240, issue of August 10.

SEPTEMBER 27. American Medical Writers' Association. Page xi, issue of July 13.

SEPTEMBER 27–29. Mississippi Valley Medical Society. Page 991, issue of December 15.

OCTOBER 12–14. American Association of Blood Banks. Page 428, issue of March 16.

OCTOBER 14–19. American Academy of Pediatrics. Page 962, issue of June 15.

OCTOBER 23–27. American College of Surgeons. Page xi, issue of June 29.

OCTOBER 23–28. Medicomilitary Symposium for Officers of Fourth Naval District. Page 34, issue of July 6.

OCTOBER 30–NOVEMBER 3. American Public Health Association. Page 240, issue of August 10.

OCTOBER 31–NOVEMBER 3. International College of Surgeons. Page 170, issue of July 27.

NOVEMBER 1. New England Obstetrical and Gynecological Society. Hotel Somerset, Boston.

NOVEMBER 5 AND 6. American Society for the Study of Arteriosclerosis. Page 170, issue of July 27.

NOVEMBER 6–8. New England Postgraduate Assembly. Hotel Statler, Boston.

NOVEMBER 10. American Trudeau Society. Page 280.

JANUARY 31. American Academy of Orthopaedic Surgery (see Kappa Delta Award for Research in Orthopedic Surgery). Page 736, issue of May 4.

APRIL 9–13. American College of Physicians. Page 962, issue of June 15.

DISTRICT MEDICAL SOCIETY

HAMPSHIRE

SEPTEMBER 6. 4:30 p.m. Belchertown State School.
NOVEMBER 1. 4:30 p.m. Northampton State Hospital.
JANUARY 3. 4:30 p.m. Veterans Administration Hospital, Northampton.
MARCH 7. 4:30 p.m. Cooley-Dickinson Hospital, Northampton.
MAY 2. 4:30 p.m. Annual Meeting. Jones Library, Amherst.

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, AUGUST 24

THURSDAY, AUGUST 24

*9:00–10:00 a.m. Grand Rounds. House of the Good Samaritan.

FRIDAY, AUGUST 25

*9:00 a.m.–12:00 m. Combined Medical and Surgical Staff Rounds. Peter Bent Brigham Hospital.

*10:00 a.m. Surgical Clinic. South End Health Unit, 57 East Concord Street, Boston.

*1:30 p.m. Tumor Clinic. Out-Patient Department. Mount Auburn Hospital, Cambridge.

MONDAY, AUGUST 28

*11:30 a.m.–12:15 p.m. Clinical Conference. South End Health Unit, 57 East Concord Street, Boston. Dr. Cleaveland Floyd in charge.

*12:15–1:15 p.m. Clinicopathological Conference. Main Amphitheater, Peter Bent Brigham Hospital.

5:15 p.m. Staff Meeting. Harris Hall, New England Deaconess Hospital.

TUESDAY, AUGUST 29

*12:15–1:15 p.m. Clinicoroentgenological Conference. Peter Bent Brigham Hospital.

WEDNESDAY, AUGUST 30

*12:00 m.–1:00 p.m. Grand Rounds. Amphitheater, Children's Hospital.

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